NOXIOUS GASES

AND THE

PRINCIPLES OF RESPIRATION
INFLUENCING THEIR ACTION

BY

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GENERAL INTRODUCTION

American Chemical Society Series of Scientific and Technologic Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in coöperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical development. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the monographs, Charles L. Parsons, Secretary of the American Chemical Society, Washington, D. C.; John E. Teeple, Treasurer of the American Chemical Society, New York City; and Professor Gellert Alleman of Swarthmore College. The Trustees have arranged for the publication of the American Chemical Society series of (a) Scientific and (b) Technologic Monographs by the Chemical Catalog Company of New York City.

The Council, acting through the Committee on National Policy of the American Chemical Society, appointed the editors, named at the close of this introduction, to have charge of securing authors, and of considering critically the manuscripts prepared. The editors of each series will endeavor to select topics which are of current interest and authors who are recognized as authorities in their respective fields. The list of monographs thus far secured appears in the publisher's own announcement elsewhere in this volume.

The development of knowledge in all branches of science, and especially in chemistry, has been so rapid during the last fifty years and the fields covered by this development have been so varied that it is difficult for any individual to keep in touch with the progress in branches of science outside his own specialty. In spite of the facilities for the examination of the literature given by Chemical Abstracts and such compendia as Beilstein's Handbuch der Organischen Chemie, Richter's Lexikon, Ostwald's Lehrbuch der Allgemeinen Chemie, Abegg's and Gmelin-Kraut's Handbuch der Anorganischen Chemie and the English and French Dictionaries of Chemistry, it often takes a great deal of time to coördinate the knowledge available upon a single topic. Consequently when men who have spent years in the study of important subjects are willing to coördinate their knowledge and present it in concise, readable form, they perform a service of the highest value to their fellow chemists.

It was with a clear recognition of the usefulness of reviews of this character that a Committee of the American Chemical Society recommended the publication of the two series of monographs under the auspices of the Society.

Two rather distinct purposes are to be served by these monographs. The first purpose, whose fulfilment will probably render to chemists in general the most important service, is to present the knowledge available upon the chosen topic in a readable form, intelligible to those whose activities may be along a wholly different line. Many chemists fail to realize how closely their investigations may be connected with other work which on the surface appears far afield from their own. These monographs will enable such men to form closer contact with the work of chemists in other lines of research. The second purpose is to promote research in the branch of science covered by the monograph, by furnishing a well digested survey of the progress already made in that field and by pointing out directions in which investigation needs to be extended. To facilitate the attainment of this purpose, it is intended to include extended references to the literature, which will enable anyone interested to follow up the subject in more detail. If the literature is so voluminous that a complete bibliography is impracticable, a critical selection will be made of those papers which are most important.

The publication of these books marks a distinct departure in the policy of the American Chemical Society inasmuch as it is a serious attempt to found an American chemical literature without primary regard to commercial considerations. The success of the venture will depend in large part upon the measure of coöperation which can be secured in the preparation of books dealing adequately with topics of general interest; it is earnestly hoped, therefore, that every member of the various organizations in the chemical and allied industries will recognize the importance of the enterprise and take sufficient interest to justify it.

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Foreword.

Gases differ fundamentally from solids and liquids in their physical behavior; a substance in volatile form may exhibit properties, even in its chemical action, widely different from those of the same substance as a liquid or a solid. Accordingly poisonous gases and vapors have characteristic effects upon men and animals exposed to them distinct from noxious substances in solid and liquid form. This book deals primarily with the special features of toxic action dependent upon volatility.

Respiration, the function of absorbing and eliminating volatile substances, differs no less fundamentally from the physiological processes by which solids and liquids are ingested and excreted. Consequently an understanding of the toxicology of noxious gases must be based on the special features of the physiology of respiration.

Owing to these considerations, the classification and description of volatile poisons are necessarily different in some respects from those usually employed in toxicology as well as from those which chemistry would suggest. Systematic description of their actions must be based in part upon their chemical character, in part upon their physical properties such as volatility and solubility, in part upon their pharmacological and toxological actions, and in part upon their special relations to respiration. The mode of classification adopted here is practical rather than strictly logical.

The literature primarily devoted to the particular topic of volatility as a factor in toxicology is small. This book is in fact the first monograph in its special field. But the literature of industrial medicine and toxicology in general is enormous, and nearly the whole of it is involved as the background of noxious gases. To refer to the entire background would swell this book to many times its present size; it would also be superfluous, for the literature of the general effects of poisons is fully summarized with references in text- and handbooks which are readily available. But these works deal chiefly with solid and liquid poisons and their entrance into the body thru the alimentary canal. It is only with the special features due to volatility and entrance thru the lungs that we are concerned. It has seemed best, therefore, to confine the references given here to two purposes: (1) particular points, usually on toxic concentrations, and (2) general references

placed at the ends of the chapters thru which the reader may find his way to works in which the original literature of industrial medicine and toxicology is reviewed and referenced. In particular we would recommend for this purpose the recently published book "Industrial Poisons in the United States," by Dr. Alice Hamilton, which presents an admirable account of this general field, and references to its literature.

Only those gases which occur in industry are here dealt with; their use in war is not discussed. References to works dealing with chemical warfare are, however, given at the end of Chapter VIII on irritant gases. It should be added—by way of "giving the Devil his due"—that immensely valuable measures of protection against industrial gases have resulted from the study of war gas defense.

As this book has been written for the practical use and information of chemists, engineers and others engaged in industry, a rather full description of the function of respiration has been included. It has not seemed necessary to give extensive references to the original articles on respiration in journals of physiology and the rapidly growing literature; but at the end of the chapters dealing with respiration a number of monographs and reviews have been cited from which the reader may obtain both an extensive survey and further references.

Physiologists may think that the discussion of respiration in the second and third chapters goes too far—for it certainly goes far beyond any current textbook—in presenting a vital function as a mechanism. Chemists, on the other hand, are prone to assume that all vital phenomena are merely physico-chemical; and by "physico-chemical" they mean the physics and chemistry of the present day. What else can they mean, unless they have the gift of prophecy? An eminent biochemist describing certain relations in the blood remarks that "a simple physico-chemical explanation has been evolved, which appears successfully to remove these complex relationships from the realm of vitalism, and to place them among the phenomena for which we consider supernatural explanations unnecessary." This implies that any explanation of a vital function which is not entirely physico-chemical is "supernatural." It would be quite as fair, and scarcely more destructive of useful knowledge and work, to charge most of the chemistry of the present time with involving supernatural explanations, because it is not as yet stated in terms of the atom as physicists now conceive it. Until chemistry has advanced far beyond its present stage, physiology will have to describe and generalize many of the phenomena in its field without attempting, however much it may desire, physico-chemical explanations. Physiology aims to avoid both supernatural and pseudo-physico-chemical conceptions. The effectiveness with which physiological principles apply to practical uses is the test of their validity.

Perhaps we should offer a few words of explanation also to the medical profession. This book treats of the medicine of volatile poisons; but it is written for chemists and engineers rather more than for medical men. The reason is that the conditions under which gas poisonings usually occur are such that no physician sees the cases until too late to influence their course materially. Chemists are in immediate contact and control. Furthermore they are increasingly responsible for the human portion of the machinery of production, and for the determination and prevention of the poisonous aspects of the products which they manufacture.

There is, however, urgent need that physicians should in general have a greater understanding of matters in this and related fields, and that they should be prepared, as they are not now, to deal intelligently and effectively with them. In fact in the matter of first aid, and especially in the administration of artificial respiration in cases of asphyxia and the related conditions of drowning and electric shock, the campaign of education carried on in recent years by the organizations interested in safety in industry has been so effective, while medical education has paid so little attention to the subject, that today policemen, electric linemen, and particularly the boy scouts frequently save lives that a physician cannot. Furthermore, interference by a physician who declares the victim dead or sends him to the hospital in a nonbreathing condition, so that he dies on the way, is believed at the present time to prevent resuscitation in a considerable number of cases.

For industrial hygiene as well as for medicine and surgery the modern knowledge of the principles of respiration holds extensive and valuable applications, many of which are still unutilized. It is the hope of the writers that the following pages may lead to a more general utilization of the information now available, and may stimulate the further development both of knowledge and of application in this field.

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NOXIOUS GASES

Chapter I.

General Survey of the Field.

The use of gases and defences against them became a subject of immense importance during the late war. Gas warfare was exceeded by no feature of military affairs. No subject caused more anxiety to national leaders, or received a greater amount of thought and investigation by scientific experts, or took a stronger hold upon popular imagination.

Gas Hazards of Industry.

The gas hazards of modern peaceful industry and defences against them are no less important. This is almost the only field in the whole range of modern sanitation in which the number of fatalities thruout the civilized world increases year by year. This increase can and should be checked. Nevertheless it is a safe prediction that long after the zymotic diseases have been controlled, or even in large part eliminated, deaths from gas asphyxiation will still occur.

The reactions between a living man and the atmosphere about him are so immediate, so continual and so much a matter of course, that the normal individual passes days or even years without a thought of breathing. Several times each day he thinks of food, and not infrequently of digestion. He is interested in the principles of alimentation; he gladly accepts scientific knowledge and takes elaborate precautions in food and drink. But of respiration and the gaseous substances which he takes into his body thru the lungs he is generally oblivious. On such matters even educated and thoughtful people are now usually uninformed. And yet the way that most people die is by cessation of respiration.

In modern industry volatile substances are used in enormous quantities. They occur as raw materials, as products, and as agents in manufacture. Chemical processes play a continually increasing part in indus-

try. Thruout the whole of modern society the products of petroleum, for instance, are articles of daily and hourly use. Substitutes and blends of other volatile substances are appearing on the market. The inhalation of gases and vapors foreign to pure air is thus almost universal. It is fortunate that not all volatile substances are extremely toxic; but comparatively few are entirely free from all drug effects.

Respiration as an Avenue of Absorption.

It is essential that the gases which may affect human life should be treated apart from harmful solids and liquids and in relation to breathing. Between the gaseous state of matter on the one hand, and solids and liquids on the other, there is not only a fundamental difference from the physical and chemical standpoints, but an even more important distinction physiologically. Solids and liquids usually enter the body by being swallowed and thus pass into the system by way of the digestive tract. Volatile substances, on the contrary, are inhaled. The toxicology of solids and liquids must be studied with the functions of the alimentary canal as a background. The actions of gases upon the body can be treated effectively only with the fullest reference to the physiology of respiration.

Respiration is fortunately a function regarding which knowledge is more nearly, so to speak, on an engineering basis than any other process of the body. We are now able to control the volume of breathing of a patient so that the ventilation of his lungs is immediately increased two to six or more times over the resting normal amount; and it may be so maintained for hours. The otherwise slow elimination of many volatile substances is thus greatly accelerated, and the period of their stay in the body and their ill effects are correspondingly reduced. It is noteworthy also that this therapeutic measure applies not merely to substances such as carbon monoxide and ethyl ether, which are absorbed as gas or vapor, but also to the elimination of such volatilizable liquids as the alcohols, both ethyl and methyl, after absorption from the stomach.

General Classification of Gases.

Viewed as problems of respiration it is possible, as we trust this book will demonstrate, to establish in regard to the actions of gases a set of broad and very practical conceptions for application to hygiene and therapy. A classification of gases merely from the chemical standpoint would not serve this purpose. Gases as distinct chemically as hydrogen and nitrogen are yet identical in their physiological action, while some of the gases which are classified together chemically are wholly unlike in the reaction which the body makes to them.

The classifications commonly used in pharmacology and toxicology are also an inadequate basis for dealing with volatile substances. While the character of the drug action is of interest, knowledge of it helps but little in the directly practical problems of preventing absorption and hastening elimination: the essentials of prophylaxis and therapy. For these problems we need to consider rather such respiratory data as the figure which defines the solubility of the gas in the blood and determines its distribution between the air and the blood in the lungs. This is the fundamental factor in such diverse matters as the rate of initiation and termination of ether anesthesia, and the development or prevention of caisson disease from work in compressed air.

From the standpoint of respiration gases may be classified as follows:

(1) **Asphyxiants.** (a) Simple asphyxiants: physiologically inert gases like nitrogen and hydrogen which when breathed in high concentration act mechanically by excluding oxygen. (b) Chemical asphyxiants: substances which by combining with the hemoglobin of the blood or with some constituent of the tissues either prevent oxygen from reaching the tissues, or prevent the tissues from using it.

(2) **Irritants.** Gases of this class injure the air passages or the lungs or both, and induce inflammation in the surfaces of the respiratory tract.

(3) **Volatile Drugs and Druglike Substances.** These gases exert little or no specific effect upon the lungs; they act after they have been absorbed into the blood and transported to the tissues of the body. Their acute effects are chiefly upon the nervous system to induce anesthesia. This group includes a large number of volatile hydrocarbons occurring in industry, whose chief action is essentially like that of the substances used for surgical anesthesia, and also the organic nitro compounds whose most characteristic action is to alter or destroy the hemoglobin of the blood.

(4) **Inorganic and Organometallic Substances.** This fourth group includes a large number of poisonous elements and compounds occurring in industry in volatile form and exerting a wide variety of toxic actions after their absorption into the body.

Plan of Presentation.

The order in which the material will be presented is as follows: Chapters II and III are devoted to a description of the principles of respiration and their practical application. Chapters IV and V describe the practical applications of the laws of gases and vapors and the principles which follow from these laws and from the nature of respiration. These principles determine the absorption, distribution and elimination

of gases in the body. Chapter VI gives a classification of the chief groups of gases based on their physiological action and a table of the gases and vapors which occur in industry listed in their chemical order, but with indications of their physiological class. Chapter VII describes the asphyxiants, and Chapters VIII and IX the irritants. Chapters X thru XIII deal with the organic volatile druglike substances and Chapter XIV with the inorganic and organometallic gases. The last chapter, XV, discusses the prevention and treatment of poisoning by noxious gases.

Chapter II.

Elements of Respiration.

The volume of air that a man breathes is usually the principal physiological factor in the amount absorbed of any gas or vapor mixed with the air. It is essential at the outset to gain a clear conception of the volume of breathing and of the underlying conditions determining this function of the body.

The volume of air breathed varies with every alteration of bodily activity, sitting, walking, sleeping, working, and running. But under each condition the man breathes precisely so much, exactly so many liters and parts of a liter of air in each minute. It is this quantity per minute which constitutes the volume of breathing or, as we shall use the term, the respiration.

This idea has at the present time only just begun to play a part in medical thought. It is still quite outside of the merely qualitative and descriptive survey of respiration which textbooks of physiology afford. Biochemists habitually neglect it, to the detriment of some of their conclusions. It is the key to the precise application of the modern knowledge of respiration to the problems of many fields. In determinations of the respiratory metabolism it is indeed customary to determine the volume of air breathed; but this measurement is used merely as one factor in the calculation of the calories expended in the body. In every hospital it is customary to count the number of breaths in a minute and to enter this on the chart with the patient's temperature and pulse. But this practice is a demonstration of the lack of a real conception of the meaning of the respiration, that is the volume of breathing; for unless this count is multiplied by a figure also for the average volume of the breaths, no effective measurement of the breathing results. What we need to know is the volume of air in liters breathed by the patient in one minute.

Erroneous Ideas of Respiration.

Breathing cannot be estimated from mere inspection. A doubling of the volume breathed per minute is scarcely or not at all noticeable either by the breather himself or by the casual observer, and it may

escape even the careful observer, unless he measures it. If the increase to double volume is induced, for instance, by a moderate increase of bodily exertion, such as an easy rate of walking, it involves no sense of effort in the subject, and no ill effect. But if a man while sitting still in normal air were to breathe double the normal amount for a few hours it would induce profound disturbance, unconsciousness and perhaps even death.

Many of the impressions which we derive from our own feelings, and are therefore inclined to accept as obvious truths, are in reality misleading or even directly contrary to the actual occurrences. Thus, for example, one who feels extremely out of breath from muscular exertion or experiences air hunger for some other reason is in fact usually breathing not less, but much more than he really needs. This is especially the case if he is out of training and in poor physical condition. Again, one who feels that the "wind has been knocked out of him" by a blow over the stomach, and that he cannot inspire, altho he strives to do so, is in fact inspiring excessively and is actually incapable for the moment of making an adequate expiratory movement. His lungs are not empty but full. An inhalation of dilute carbon dioxide produces a considerable augmentation of breathing; but the subject often complains "I can't get my breath,"—the exact opposite of the reality.

To the individual himself breathing seems to be an activity which is nearly as much under voluntary control as walking or talking. By a slight effort of attention he can regulate the rate of his breathing to only four or five times in a minute, or twenty to thirty times, or any intermediate number. Thus in talking and singing the breath is controlled to afford the proper current thru the vocal cords. Likewise emotions, pleasurable and painful, induce those forms of breathing of which laughter and weeping are the manifestations. We all perceive these occurrences and infer that breathing is controlled to a great extent at least by the will.

Such observations upon one's self are, however, wholly misleading as regards the volume of air breathed in any considerable period. Over this volume one has practically no voluntary control or at least he ordinarily exercises none. When by exercise of will one breathes a greater or less number of times per minute, the involuntary mechanism of respiration compensates by making slow breathing deep, and by making rapid breathing shallow. The total volume of air inhaled and exhaled during a certain period is neither controlled by the will nor greatly influenced by the emotions, but is adjusted so as to maintain the body's interior atmosphere as nearly constant as possible. In health it is the expenditure of energy in muscular work which tends especially to alter

the interior atmosphere, and thus to increase the volume of air breathed, to compensate the alteration and restore the normal.

The Volume of Breathing.

Respiration, as the term will be generally used in this book, is the volume of air which is inspired and expired in one minute. It is expressed in liters at the prevailing temperature and barometer. It is most accurately measured by means of a mouthpiece or mask, fitted with very light valves of mica or rubber so that the stream of air to or from the mouth passes thru some measuring apparatus. This apparatus may be a gas meter either wet or dry. Or the air may be drawn from or collected in a spirometer (gasometer). Or it may be caught in a large rubber bag, called a Douglas bag, and then metered. A simpler method, especially applicable to unconscious persons, or when only this one measurement is wanted, is the use of a small spirometer of about five liters capacity and graduated in 0.01 liter, which is connected with a tight-fitting face mask without valves. The breath causes the bell of the spirometer to rise and fall thru a distance which indicates the volume of the tidal air; and this quantity multiplied by the number of breaths for a minute usually affords a sufficiently accurate indication of the respiration. Not more than three or four breaths at a time should be thus measured, for the rebreathing of the air in the spirometer for a longer period induces an increase in the breathing because of the vitiation of the air.

Structure of the Lungs.

For a complete description of the lungs, reference should be made to a textbook of anatomy, but the structure is best understood from an examination of the lungs of an animal freshly killed. Those features of the lungs which particularly concern us here are as follows:

The lungs (see figure 1) are composed of a great number of minute saccules which are further divided by delicate partitions into the ultimate air spaces termed alveoli. These saccules form the terminal dilatations of very small air tubes called bronchioles. The bronchioles are branches of larger tubes, the bronchi, which in turn unite to form still larger tubes; at the medial surface of the lungs and directly behind the heart, these tubes open into the trachea or windpipe. This large tube with walls stiffened by incomplete rings of cartilage extends upward and terminates in the pharynx, or upper part of the throat. Thus there is free access for atmospheric air to the lungs thru the nose and mouth, except momentarily when the glottis is closed during the acts of swallowing or coughing. The smaller tubes are provided with muscular walls and under irritation may contract and prevent the passage of air

into the area of saccules and alveoli supplied by them. The trachea, bronchi and bronchioles are lined with mucous membrane and are capable of secreting fluid upon their surface. The entire system of tubes takes very little part in the exchange of gases; it merely affords passage to and from the terminal air sacs.

The alveoli have exceedingly thin walls of delicate elastic framework, almost completely filled with a network of capillary blood vessels, and covered only by an extremely thin membrane. It is between

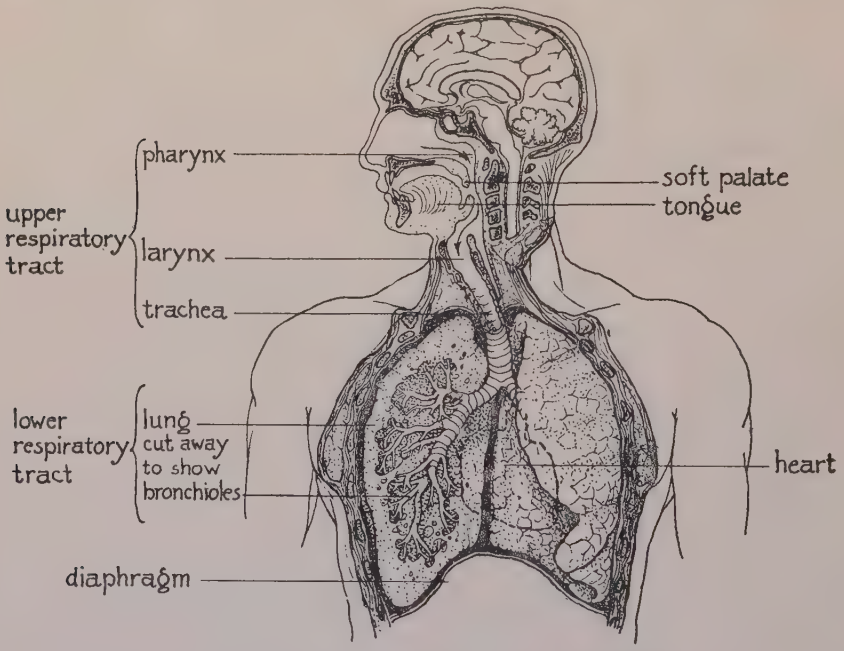

Fig. 1.—Showing anatomical relations of the respiratory tract.

the blood in these vessels and the air in the alveoli that gaseous exchange takes place. Owing to the thinness of the walls and to the enormous total surface of the capillaries (estimated at 90 square meters in the lungs of man), the process of diffusion of gases is so rapid that a virtual equilibrium of the partial pressure of every gas in the saccules is almost instantly established between the blood in the capillaries and the air in the alveoli. It is an amazingly effective equilibrating apparatus. As we shall see, however, it is specially arranged to effect equilibrium, not with the outside air but with the special atmosphere of the lungs.

The blood is supplied to both lungs thru arteries from the right heart which enter alongside of the bronchi. From this point the vessels divide

and subdivide until they form the alveolar capillaries. From the capillaries onward the blood vessels unite again into increasingly larger vessels, and these pulmonary veins finally emerge near the point of entrance of the bronchi and pass to the left side of the heart. The lung has normally but one attachment in the body, which is that on the medial surface where the bronchi and blood vessels enter. At all other points the lung is freely movable within the chest cavity.

The entire structure of the lung is extremely elastic. In a lung which has been removed from the body the saccules contract until they are almost collapsed and contain only a very small amount of air. In the body this collapse is prevented by the fact that the lungs are encased in the airtight and comparatively rigid walled cavity of the thorax. There is no air in the potential space between the chest wall and the lungs, and only a little fluid, by which the walls are moistened sufficiently for lubrication. Since the interior of the lungs is in communication with the outside air thru the trachea, the elasticity of the saccules is overcome by the pressure of the atmosphere and the lungs are inflated, so that they completely fill the thoracic cavity and are held tightly against the chest walls. By the same mechanism any movement of these walls, resulting in an increase or decrease of size, results in a like change in the volume of the lungs which are thus expanded or contracted in exact conformity to the size and shape of the chest cavity. As a result, air passes in and out of the air sacs and alveoli and thru the trachea, thus producing the tidal movement of the air in and out of the nose and mouth.

As all of the sacs open freely thru the communicating tubes into the trachea and are of exactly equal elasticity the inspired air is generally shared nearly alike by all parts of the lungs. Were the alveoli of one section of the lungs to receive more air than others they would be put under a greater elastic stretch, and the strains would then tend to equalize as in any physical system. The only unequal distribution of air in the lungs results from the friction of the air in passing to those saccules which are supplied by the longer tubes. For this reason the areas nearest the stalk of the lung, where the bronchus enters, expand first and the more distant areas only an instant later. The lungs thus open out somewhat after the manner of a fan. In ordinary full slow breathing there is sufficient time for a general equalization of the air thruout the lungs. In very shallow and rapid breathing there may not be sufficient time for this equalization, and in consequence an unequal distribution of the air results and produces an imperfect or fractional aëration of the lungs and of the blood which passes thru them, excessive at one point and incomplete in others (see also page 26).

The surface of the lungs is covered by a thin layer of smooth tissue,

the pleura. Similar tissue lines the inner surface of the chest wall. These two pleural surfaces slide over each other during the various movements of the thorax. The surfaces of the lungs may slide upon the chest wall as much as seven or eight centimeters, or even more at some points distant from the lung stem, when a deep breath is drawn and then fully exhaled.

The changes in the volume of air in the lung are brought about thru movements of the diaphragm and ribs. The diaphragm is a sheet of muscle convex toward the thorax and separating that cavity from the abdomen. Its contraction increases the length or height of the cavity; while an upward movement of the ribs, owing to the direction in which they are hinged on the spine, increases the cross-section of the chest, especially transversely. All the movements of inspiration are due to muscular contractions induced by nervous impulses. Expiration is a less active process, for when the muscles relax the elasticity of the lungs themselves tends to drive out the air previously inhaled. This action is assisted by the weight of the thorax in the standing and sitting positions, and by the weight of the liver and stomach upon the diaphragm when the person is lying upon his back.

Owing to our being in the habit of doing work in overcoming the elastic pull of the lungs during inspiration, but not during expiration, we find that in the use of respiratory apparatus a resistance to inspiration amounting to a negative pressure of 3 or 4 or even 5 or 6 cm. of water can be tolerated for some time; but a resistance to expiration of a positive pressure of more than 2 cm. of water soon becomes distressing. When the resistance arises from irritation and inflammation with consequent narrowing of the air tubes of the respiratory tract, expiration is liable to be much more noticeably impeded than inspiration. The lungs become stretched and a chronic condition, termed emphysema, results.

When the volume of breathing is increased by physical exertion many accessory muscles are called into action to assist in inspiration; and expiration involves then also a vigorous action on the part of the abdominal muscles.

Mechanism Controlling Rhythm of Breathing.

For the effective and uniform ventilation of the lungs it is necessary that air should be drawn in and again discharged by a rhythmic alternation of contractions and relaxations of the respiratory muscles. The mechanism is of the type that an engineer calls "reciprocating." Such mechanical devices as the continuously revolving wheel, or the turbine, or rotary pump, are not found, and probably are not feasible in an organism. There is, however, a very perfect type of arrangement

for insuring such reciprocating acts as walking, chewing, breathing, and in some animals the wagging of the tail. For such actions the bones are utilized as levers in a multiplicity of forms.

The movements of the ribs, like those of the arms and legs, are typical of such levers. The physiological mechanism always includes two antagonistic muscles or sets of muscles tending to move the part in opposite directions. For the mechanism to act so as to flex and then extend a joint, or to inspire air and expire it again, it is necessary that one of these muscles or sets of muscles should relax while the other contracts, and then that the first should contract while the latter relaxes. The relaxation is almost as essential as the contraction, and the accurate timing of the alternation is essential for rhythm and efficiency.

During normal life such mechanisms are never either jammed or dead centered, but the actions reciprocate with extraordinary precision. The reason for this precision, and particularly for the alternation of inspiration and expiration, does not lie in any mechanical arrangement of bones and muscles or other mechanical parts as in a steam engine, but in the nerves and centers controlling the movements, somewhat as in the electrical sparking apparatus in a gasoline motor.

The nerves and centers of respiration are of exactly the same type as those of all the other so-called voluntary muscles of the body. In all voluntary acts such, for example, as walking and chewing, and even in such acquired motions as playing the piano, there is a very large involuntary element; and in respiration the involuntary element is relatively greater than in nearly any other muscular action. The rhythm and reciprocating action of breathing are most of the time almost wholly involuntary.

The motor nerves come from centers in the spinal cord and carry the impulses causing both tonus and active contraction. Along with these motor or efferent fibers run also the sensory or afferent fibers which conduct impulses in the opposite direction and, so to speak, inform the centers of the state of the muscles from which they come. If there is at the moment no excitement or stimulation flowing down from the higher nerve centers of the brain to cause the mechanism to act, the afferent nerve fibers from the muscles themselves, their "representors," influence the motor centers to produce in the muscles a state of tonus.

It is this state of rubberlike or springlike elasticity, with a minimum expenditure of energy in contrast to active contraction, which maintains the erect standing position. The state of tone in the muscles of the chest does not wear off entirely for 10 or 15 minutes after breathing has stopped; and this residual elasticity makes it possible by means of manual artificial respiration, if promptly applied, to resuscitate a man drowned or one shocked with electricity. After the muscles lose

their tonus and become flaccid, manual artificial respiration is ineffective in causing air to enter and pass out of the chest. Simultaneously with, or some minutes before, this loss of tonus the higher centers in the brain are irreparably damaged by lack of oxygen, and life is therefore irretrievable.

When such a neuromuscular mechanism passes from mere tonus into rhythmic action, the representors play an even more important rôle. Thus any muscle which is contracted tends thru the influence of its representor to act upon its own motor center to shut off the flow of stimulation from itself, and to divert activity into its antagonist. The contracted muscle is thus allowed to relax, and the relaxed muscle is stimulated to contract; and then the action reverses. Thus a reciprocating mechanism like respiration (or walking, or the wagging of an animal's tail) tends to continue automatically acting and reversing so long as any excitement flows into its centers.

Besides the usual representors of individual muscles, respiration is provided with a special pair of afferent nerves, the pulmonary branches of the vagi, coming from the lungs themselves. These nerves pass up thru the neck and enter the medulla oblongata, or spinal bulb, the lower part of the brain, in the tenth cranial nerve. At about this level lies the so-called respiratory center, consisting probably of a series of complicated nerve connections, a sort of telephone switchboard, which integrates, controls, and coördinates the activities of all of the spinal centers of the nerves to the respiratory muscles. Upon this respiratory center the vagus nerves exert an influence of the representor type.

Thus when an inspiration has occurred and the lungs are stretched the vagal endings in the lungs are stimulated, so that nervous impulses are transmitted to the respiratory center. There they inhibit the inspiratory actions and induce expiration. Conversely the partial deflation of the lungs by expiration induces inspiration. When either phase is opposed by obstruction to the flow of air (as with some gas masks and other breathing apparatus), that phase tends to be prolonged and to intensify muscular effort; instead of inducing an immediate reversal of phase. Thus a slight resistance to the free flow of air in and out of the lungs tends to induce a slower and deeper form of breathing. When such respiration is desired it is most easily attained by breathing against a slight positive pressure as, for instance, from and into a large rubber bag, or a spirometer suitably weighted.

Irritation of the Lungs and Shallow Breathing.

The details of the experimental evidence concerning this function of the vagi do not concern us here. But it is of great practical importance to note that any continuing irritation in the lungs, as in pneumonia or

from an irritant gas, tends to induce a rapid alternation of inspiration and expiration, and a correspondingly shallow form of breathing. This results, as explained above, in the ventilation of only a part of the lungs. Thru the unventilated parts the blood passes with little or no gain of oxygen or decrease of carbon dioxide. If the blood flowing thru the ventilated area is somewhat over-aërated and its carbon dioxide content thus reduced below normal, the mixed arterial blood flowing onward to the body is the average of the two fractions and may have a nearly normal content of carbon dioxide. The mixed arterial blood is, however, incompletely oxygenated because of the fact that the over-ventilated fraction of the blood cannot take up more than its hemoglobin content allows, while the other fraction is not oxygenated. The patient is therefore cyanotic (blue), and he may exhibit other symptoms of oxygen deficiency.

Volume of Breathing and Respiratory Exchange.

The volume of air breathed by a normal man at any time is dependent upon, and is the mathematical product of, two conditions or sets of conditions: (1) the amount of oxygen that he is consuming and the amount of carbon dioxide that he is producing, and (2) the ratio of ventilation to oxidation, the dilution factor, at which his breathing is set. In fact, leaving aside for the moment certain details and assuming a constant dilution ratio, the volume of air breathed per minute by healthy men is within moderate variations proportional to the respiratory exchange in the ratio of 25 : 1 or 100 : 4 for carbon dioxide and 20 : 1 or 100 : 5 for oxygen. In other words, the inspired air contains 21 per cent of oxygen, while the expired air has lost 5 per cent of oxygen and gained 4 per cent of carbon dioxide. These relations hold true with very slight changes alike when a man is lying in complete rest, and when he walks and the volume of breathing and the oxygen consumption and carbon dioxide elimination are doubled. Even when he works fairly hard and they are multiplied several fold, the volume of breathing so nearly keeps pace with the combustion going on in the body that the carbon dioxide in the expired air only rises to about five per cent. But the relation is disturbed by very vigorous exercise; and especially in men in poor training any considerable exertion causes heavy panting so that the elimination of CO_2 rises out of proportion to the oxygen absorbed, and the volume of breathing increases out of proportion to the gaseous exchange.

Respiratory Quotient.

That five volumes of oxygen are consumed for each four volumes of carbon dioxide produced is due to the fact that about one-fifth of

the oxygen is usually expended in oxidizing elements other than carbon, especially the hydrogen of fats and the sulfur of proteins. The relation of the volume of carbon dioxide produced to the volume of oxygen consumed, that is $\frac{CO_2}{O_2}$ is called the respiratory quotient and is indicated by the letters R.Q. It is often used as an index of the foodstuffs which are being consumed as fuel in the body. Carbohydrates such as starch ($C_6H_{10}O_5$), or cane sugar, ($C_{12}H_{22}O_{11}$), produce as many molecules of carbon dioxide as the molecules of oxygen consumed in their combustion, and have therefore an R.Q. of 1.00. Proteins consumed in the body give an R.Q. of 0.78 to 0.81, and may be distinguished from a mixture of carbohydrate and fat by determining the amount of the nitrogen excreted in the urine. Each gram of nitrogen comes from the decomposition of about 6.3 grams of protein. The fats of the food have an R.Q. of about 0.7. On a mixed diet, but after the immediate effects of a meal have passed off, the R.Q. generally approximates 0.8.

The R.Q. is, however, often quite misleading as an index of the character of the combusion at the moment. Its evidence on this matter is reliable only under resting conditions, and in subjects trained to experiment, or when the subjects are observed over considerable periods of time. Any excitement, such as that from being the subject of an experiment, may cause temporary over-breathing. This increases the elimination of carbon dioxide from the preformed carbonic acid and bicarbonates in the blood considerably, altho only temporarily, but it does not affect the oxygen consumption appreciably. During very hard work there may be a temporary deficit of oxygen consumption below the interior need, but an excessive elimination of CO_2. The deficits both of oxygen and of CO_2 are made up during the subsequent rest. These temporary disturbances of equilibrium distort the R.Q. while they last, but they are always compensated subsequently. A true index of the fuel consumed is obtainable from the R.Q. only when the period of observation is sufficiently prolonged.

Dilution of Respiratory Gases.

More important to our present purpose is the relation of the gaseous exchange, the oxygen consumed and the carbon dioxide produced, to the minute volume of respiration. This depends upon the principle of dilution. Thus if a definite amount, such as one gram of some substance, is dissolved in a certain volume of some liquid, such as a liter of water, and then in two liters, and then in three and so on, the percentage of the solute varies inversely as the volume of the solvent. The dilution factor, which is of fundamental importance in respiration, rests on the same principle. If a man is producing 0.3 liter of carbon

dioxide and breathes twenty-five times as much air, or 7.5 liters, the dilution is 25 : 1, and the expired air will contain 4 per cent of carbon dioxide. If the carbon dioxide production continues to be 0.3 liter, but in exhaling it he breathes 15 liters of air, the dilution ratio is 50 : 1, and the expired air contains 2 per cent carbon dioxide. If, however, he breaths only 3.75 liters the ratio is 12.5 :1 and the percentage of carbon dioxide rises to 8.

There is then a factor in the body which sets, and holds at a certain setting, the exact degree to which the respiratory exchange is diluted by the volume of breathing; but this factor, the blood alkali, and its control we must leave for fuller discussion in the next chapter. What needs to be emphasized now is that during health and at sea level this factor is uniform for the individual, and the dilution is therefore nearly the same thruout the wide variations of respiratory exchange incident to bodily rest and moderate work. The conditions in the body determining the exact mass of carbon dioxide for elimination at each instant are quite distinct from the conditions determining the dilution ratio.

Relation of Oxygen and Energy.

The consumption of oxygen is not only a fundamental requirement for any considerable bodily exertion, as well as for heat production during rest, but fortunately for purposes of calculation there is also a quantitative relation of oxygen to energy. A liter of oxygen consumed in the body produces an amount of energy which, expressed in heat units, is always very close to 4.8 Calories for a person on the ordinary American diet. On a diet of pure fat it would be 4.69 Calories per liter of oxygen, and on one wholly of carbohydrates 5.05 Calories per liter. The oxygen consumption and the energy expenditure of the body are therefore at all times so nearly proportional that for many purposes the correspondence may be treated as if it were invariable at the ratio of one liter of oxygen to 4.8 Calories.

Energy Expenditure and Volume of Breathing.

Thus it follows that, as the oxygen consumption of the body at any time is nearly proportional both to the energy expenditure and to the volume of breathing, the two latter functions are nearly proportional to each other. It is, therefore, the energy expenditure which must be multiplied by a factor for the dilution ratio, a factor nearly constant for the individual under ordinary conditions. The product of this factor and the energy expenditure determine the volume of breathing. Every physical exertion, however slight or great, involves a corresponding increase of energy expenditure, increase of oxygen consumption and carbon dioxide production and a closely proportional increase

in the volume of breathing. Even rising from a sitting to a standing position costs nearly one (kilo) Calorie; sitting up in bed, about a half a Calorie, and even the lifting of a hand costs an appreciable amount. An athlete in a Marathon race or any equivalent and prolonged exertion may maintain an expenditure of ten, or more, times his basal rate. The maximum for a few minutes of most intense exertion is about twenty times the basal rate at rest in bed before breakfast.

The energy expenditure, oxygen consumption and volume of breathing of an athletic man of about 68 kilos (150 lbs.) weight under different conditions are roughly as follows:

	Calories per Minute	Oxygen Consumption Liters per Minute at 0° C. and 760 mm.	Volume of Air Breathed Liters per Minute at 20° C.
Rest in bed, fasting.....	1.15	0.240	6
Sitting	1.44	.300	7
Standing	1.72	.360	8
Walking 2 miles per hour...	3.12	.650	14
Walking 4 miles per hour...	5.76	1.200	26
Slow run	9.60	2.000	43
Maximum exertion	14 to 20 +	3.000 to 4.000	65-100

Variations of 10, or even 20 per cent from these figures occur in different individuals according to the dilution ratio at which their respiration is set. One (kilo) Calorie is about 4 British thermal units.

Size of Body, Rate of Metabolism, and Volume of Breathing.

The energy expenditures of the body are most easily conceived as chargeable under two main items. One is the so-called basal metabolism or the expenditures for the maintenance of life, the work of the heart, movements of the respiratory muscles, the activity of the digestive apparatus, muscle tonus, and the resting heat production. This basal expenditure is for practical purposes calculated from measurements of the oxygen consumption during rest in bed several hours after a meal. The other item includes all the expenditures incident to bodily activity. The normal basal rate for adult men and women of 20 to 40 years varies roughly with their weights and quite accurately in proportion to their skin areas. In children the basal expenditure per unit of body surface is larger than for adults, and the ratio of surface to mass (weight) is greater, as geometry requires of bodies of similar shape but different sizes. For both of these reasons the respiratory exchange and volume of breathing of children are proportionately greater, and the rate at which they absorb any foreign gas is correspondingly more rapid.

Practical advantage is taken of this fact in mine rescue operations. Small animals, such as mice and canary birds, are carried with the rescue party and are used as indicators of bad air; owing to their relatively greater surface, metabolism, and breathing, they are affected much more quickly than the men carrying them.

Control of Vital Combustion.

From the various relations thus indicated it may be concluded, and direct experiment fully confirms the conclusion, that in the living body it is the energy expenditure which determines the oxygen consumption and carbon dioxide production, instead of the oxygen supply determining the combustion, as in the case of an ordinary fire. Even the inhalation of pure oxygen does not at all increase the vital combustion and amount of oxygen consumed. No less striking is the fact that when the oxygen tension in the air breathed is progressively reduced and asphyxia is developing, altho profound disturbance of bodily and mental functions and even unconsciousness occur, the amount of oxygen absorbed and consumed is not considerably decreased until death is imminent. We shall see that the pressure of oxygen breathed is a fundamental condition influencing respiration, but the effect is very slow. Life does not flare up and die down as a fire does when the draft of air is varied. For practical purposes a lighted candle usually indicates air which contains sufficient oxygen for a man to breathe safely. But experimentally it is not difficult to arrange conditions in which a candle is extinguished but a man is well, or again conditions in which the candle burns fairly well and the man collapses from want of oxygen. (See page 61.)

It may be concluded also, and again correctly, that the comparatively slight variations in the composition of the expired air, even under wide variations of physical activity and total mass of gases exchanged, indicate that in some way it is slight variations in the expired air, or in some related condition, which induce the enormous variations that occur in the volume of breathing. Before considering more closely the details of the regulation of breathing we must deal a little more precisely with certain other matters.

Respiratory Dead Space.

Not all the air inspired reaches the lungs. Part of it does not pass beyond the mouth, windpipe, and bronchi; and this air of the anatomical dead space takes little or no part in the respiratory exchange and is exhaled almost unchanged. It can be shown also that the finer air tubules in the lungs and perhaps even the centers of the air sacs themselves may contribute to the dead space. As these air sacs are elastic

and are enlarged by deep breathing, the functional or so-called "virtual dead space" is not a constant absolute volume, but is relatively about one-third of the volume of the breath both in deep and moderate breathing. When a low concentration of a gas of high solubility in blood, such as ethyl ether, is inhaled in air, nearly all of it that reaches the lungs at first is absorbed; but the mixed expired air still contains approximately 33 per cent as much of the gas as the inspired air. This amount comes from the dead space, and affords the most convenient means of estimating its volume in relation to that of the breath; for the concentration in the mixed expired air divided by the concentration inspired equals the fraction of the breath which does not reach the lungs.

True Pulmonary Ventilation.

Much of what has been said above regarding the volume and composition of the air breathed and expired really applies more strictly to the true breathing or pulmonary ventilation. Since the dead space is about 33 per cent of each breath, the volume of air which actually enters the lungs is about 66 per cent of the volume of respiration. For this same reason, the air in the lungs has a concentration of carbon dioxide which is about 1.5 times the concentration in the mixed expired air. It is this lung air primarily which is kept at a nearly uniform composition by variations of the volume of respiration. These variations are nicely adjusted to the amount of carbon dioxide produced; and the production depends upon the energy expenditure at the moment.

The composition of this lung air is indeed one of the most important of the so-called physiological constants. But its constancy, or rather its variations within narrow limits around a mean value, depends upon the continual adjustment of the volume of pulmonary ventilation to the amount of energy expended at the time and the corresponding combustion and gaseous requirements in the body. We may now consider how his adjustment is effected.

Influence of Oxygen on Breathing.

It might be expected that as oxygen is fundamental to any continued expenditure of energy, respiration would be continually adjusted and controlled by the tension of oxygen in the lungs and blood. This, however, is not the case. Oxygen is indeed, as we shall see, the fundamental controlling factor in the adjustment of breathing. Every healthy person is acclimatized and breathes a volume of air adjusted to the altitude at which he resides, be it sea level or on a mountain height, where the partial pressure of oxygen is reduced in proportion to the barometric pressure. Another indication of the influence of oxygen on respiration is the fact that a sudden acute deprivation of oxygen induces a

great augmentation of breathing. But in the ordinary variations of respiration from minute to minute thruout the day, when we sit or sleep or walk or work or run, oxygen takes little part in the regulation.

Smallness of Oxygen Reserve.

It would indeed be unfortunate and would afford a very jerky, discontinuous, waxing and waning sort of respiration, like the Cheyne-Stokes respiration of persons with heart disease, if respiration were usually regulated directly by the demand for oxygen. For a steam engine to run smoothly a heavy flywheel is needed. For a physiological function to hold nearly steady it must be, as the current expression puts it, well buffered. The whole reserve supply of oxygen in the body is small; equivalent to only five or six minutes' consumption. During ordinary breathing, the lungs contain about 3.5 liters of air with 16 per cent or 0.56 liter of oxygen. The volume of blood in the body is about 5 liters; arterial blood contains about 19 per cent of oxygen and venous blood about 15 per cent; so that the total is only about 0.9 liter, or barely five minutes supply even for resting conditions. Thus a slight absolute decrease of the oxygen in this reserve is large in per cent of the whole; and when oxygen deficiency does occur, as in heart disease, it becomes an immediate controlling factor. Under such conditions, as Haldane has well phrased it, respiration behaves like an engine with a delicate governor and a light flywheel, or a very small one, which alternately races and slows down. But in fact in normal men oxygen deficiency rarely occurs, and respiration exhibits surprisingly little immediate sensitiveness to slight variations in the oxygen content of the air breathed.

Carbon Dioxide as the Regulator of Breathing.

Respiration is, however, exquisitely sensitive to even slight variations in the concentration or partial pressure of carbon dioxide in the air of the lungs, and thus in the amount of carbonic acid in the blood passing thru the lungs. In fact the adjustment is so precise that the slightest increase or decrease of carbon dioxide production in the body induces immediately an almost proportional increase or decrease of the volume of breathing. Respiration thus almost exactly compensates any tendency for the concentration of carbon dioxide in the lungs to rise or fall more than a minute amount above or below the normal. The natural result, and in a physiological sense the purpose of this regulation, is that a nearly uniform concentration of carbon dioxide is maintained in the lungs, and thus in the arterial blood. The adjustment is so delicate and so flexible that it is maintained even under wide variations of bodily activity and of the three proportional functions, energy expenditure,

respiratory exchange of gases with the atmosphere, and volume of breathing.

Amount and Functions of Carbon Dioxide Reserve.

It is of great advantage for the smooth working of breathing that the immediate control is vested in carbon dioxide rather than in oxygen. The blood normally contains, in the form of sodium bicarbonate ($NaHCO_3$), 50 volumes per cent of carbon dioxide, or even a little more, and the tissues are supposed to hold considerable amounts. Thus the mass of carbon dioxide normally held in the body is large as compared with oxygen. Moreover, carbon dioxide is not merely a waste product; but, as modern investigations have shown, it plays a primary part in determining the normal balance of acids and bases in the blood and other body fluids. Its tension must be maintained at 40 to 45 mm. and its concentration (in the forms of dissolved CO_2, H_2CO_3, and chiefly as $NaHCO_3$) at 50 to 60 volumes per cent; otherwise the blood becomes abnormal.

Volume of Air in Lungs.

The lungs also afford a large buffer or steadying influence. They do not contain atmospheric air, but an atmosphere of a quite different composition; a composition which is also quite definite, and is constantly and carefully maintained. How this composition of the pulmonary or, as it is usually called, alveolar air is maintained can be inferred from the merely fractional character of the ventilation of the lungs. Even the deepest possible expiration leaves in the lungs still about 1.5 liters of air, the so-called residual volume. An ordinary expiration leaves in them perhaps as much more. This supplemental air plus the residual together constitute the so-called stationary air. The tidal air of quiet breathing is 0.3 to 0.6 liter of which, as we have seen, only two-thirds reach the lungs; the other third not penetrating beyond the dead space and therefore not participating to any considerable degree in the respiratory exchange. In the deepest inspiration about 1.5 liters more, the complemental air, can be drawn in. The sum of the supplemental tidal and complemental volumes is the "vital capacity," and is determined from the individual's maximum respiratory effort, the volume that he can expire into a graduated spirometer. The amount of the vital capacity in normal persons is a function of their size or weight, and particularly of the skin area, but is decreased in some conditions of disease, particularly those of the heart.

Fractional Ventilation of the Lungs.

From these data we see that respiration does not draw atmospheric air directly into contact with the blood, for it would thus bring the gas

pressures in the blood momentarily to an equilibrium with the outside air, and then during expiration would allow the oxygen to fall and the carbon dioxide to rise considerably. The lungs are particularly adapted to prevent this. At each inspiration during bodily rest only 0.2 to 0.4 liter of fresh air enter the lungs, and this fresh air is instantly mixed with the stationary air which has the alveolar composition above referred to and a volume of about three liters. At expiration 0.2 to 0.4 liter of this mixture are thrown off. Its composition is only slightly altered by the diffusion of oxygen into, and of carbon dioxide out of the blood, because of the large volume of air in the lungs. Thus the concentration, or pressure of carbon dioxide in the lungs varies only slightly during each cycle, only 0.1 or 0.2 per cent of CO_2 from a mean, which in a healthy man, adjusted to sea level, is about 5.5 per cent of an atmosphere; and the pressure of oxygen is equally constant at about 15 per cent.

During physical work and deep breathing the tidal air may increase to 1.0 or 1.5 liters or even more. But this is gained chiefly by drawing in more of the complemental air, or deeper breathing, and only to a lesser degree by more complete expirations. Thus the ventilation is still merely the mixing of perhaps 1.0 liter of fresh air with three times as much pulmonary air, and the throwing off of 1.0 liter of the mixture, while the gaseous exchange is continuous, so that the composition of the pulmonary air is kept remarkably close to its mean.

How Carbon Dioxide Insures the Supply of Oxygen.

In the ordinary conditions and activities of life every movement of the body or limbs results in the production of an increased amount of carbon dioxide and requires the absorption of an amount of oxygen corresponding to the energy expended. The carbon dioxide thus produced diffuses from the active muscles into the blood, by which it is carried to the so-called respiratory center controlling the activity of the muscles of the chest and diaphragm, and stimulates this center to increased activity. The increased respiration supplies the oxygen needed to make good the deficit, or "oxygen debt," due to the muscular work. Thus, as was first pointed out by Miescher, "carbon dioxide spreads its protecting wings over the oxygen supply of the body."

These relations and the distinction between oxygen and carbon dioxide as respiratory stimulants are best understood by considering such simple experiments as the following: A normal man at rest is given pure oxygen to breathe instead of air. This is most conveniently accomplished by means of a face mask or mouthpiece with valves connected to a spirometer from which he inhales. We look for some effect upon the rate or volume of breathing or upon the amount of oxy-

gen consumed; but we find practically none. In particular his respiration is not at all affected, or so slightly decreased that the difference is detectable only by very accurate measurement. He feels no difference between pure oxygen and air which contains only 21 per cent of oxygen. Evidently, as already pointed out, the oxidation in the tissues and the oxygen consumption of the body are controlled by conditions quite different from those determining the intensity with which a fire burns.

If now we do a second experiment with the same apparatus and method, but using air to which a small percentage of carbon dioxide has been added, the volume of the breathing almost immediately increases. In healthy subjects, unless the carbon dioxide is quite strong, the increase occurs principally in the depth of breathing without increase of rate. If we accumulate the expired air in another spirometer and measure and analyze it, we find that the body still gets rid of nearly the same amount of carbon dioxide as before, or even slightly more because of that produced by the muscular exertion involved in the greater volume of breathing. But except for this addition, the volume is still exactly adapted to eliminate just as much as and no more than the amount of carbon dioxide produced in the body. The carbon dioxide can neither increase nor decrease considerably because carbon dioxide is itself the regulating stimulus for breathing.

A third experiment of a slightly different character illustrates the dependence even of normal breathing upon the stimulus of carbon dioxide. The subject for perhaps half a minute voluntarily forces himself to breathe more deeply and at least as rapidly, but not much more rapidly than he naturally would. (The reader should try this. It is quite safe.) By this procedure the lungs are over-ventilated. Owing to the nature of the combination of oxygen in the blood (to be explained hereafter), no considerably greater amount of this gas is taken up. But the carbon dioxide content of the blood is temporarily decreased. When the voluntary effort is discontinued there occurs in most persons a striking phenomenon. It consists in an entire lack of desire to breathe and a correspondingly complete cessation of respiration. The duration of this apnea vera, as it is called, varies with the duration and intensity of the preceding over-breathing.

Even more definite evidence regarding the primary rôle of carbon dioxide in the immediate regulation of respiration has been afforded by Haldane and his co-workers. Haldane and Priestley showed that true alveolar lung air can be obtained as follows: At a time when one has been breathing naturally, a very sudden deep expiration is made thru a piece of hose (1.5 cm. diameter and about a meter in length); and the tongue is held against the upper end of the hose, while a sample of the last part of the air expired is drawn from the upper end of the hose

thru a side tube. This sample is air from the deepest parts or alveoli of the lungs. Now a series of determinations of the carbon dioxide content of alveolar air shows that in a healthy man there is an extraordinary constancy in the alveolar carbon dioxide under widely different conditions of exertion and breathing, and even when the series is extended over months and years. Thus the fundamental conceptions of the modern theory of the immediate control of respiration are: First, the regulation of the breathing to the volume necessary to maintain a nearly uniform alveolar partial pressure of carbon dioxide in the lungs; and second, the action of the carbon dioxide of the arterial blood upon the respiratory center to effect this regulation.

Contrast Between Carbon Dioxide and Deficiency of Oxygen as Stimulants.

The emphasis thus placed upon the regulation of respiration by carbon dioxide under the normal variations of life must not, however, make us overlook the influence of oxygen under abnormal or even slightly unusual conditions. Inhalation of air enriched with oxygen, or even of pure oxygen, induces, as already stated, no immediate perceptible effect or only a very slight decrease in the volume of breathing. On the other hand, the inhalation of a few breaths of an inert gas such as nitrogen or hydrogen, with little or no oxygen, induces a greatly increased or even violent breathing. This effect is nearly instantaneous. If normal air is supplied immediately afterward, the excessive respiration continues for only a few breaths. Then, instead of returning at once to normal breathing, the subject exhibits a respiration of subnormal volume or even stops breathing altogether for a short period. The explanation of this fact is that during the hyperpnea induced by the deficiency of oxygen, the elimination of carbon dioxide is augmented far above normal. When oxygen is again obtained the temporary deficiency of carbon dioxide is such as to produce apnea (cessation of breathing) or at least subnormal breathing, until the normal amount of carbon dioxide reaccumulates in the blood and in the lungs. Thus oxygen may act as a respiratory depressant and retard the elimination of some foreign or poisonous gas which has caused excessive breathing. But this depressant influence of pure oxygen may be overcome by using oxygen to which a small amount of carbon dioxide has been added.

When the deficiency of oxygen is only slight, the increase of breathing is also slight or, for a short time, does not occur. Owing to the character of the combination which oxygen makes in the blood, the effect of a progressive decrease of the oxygen in the air is at first slight; it does not become marked until the partial pressure has fallen from the normal of 21 per cent to about 13 per cent of an atmosphere, which

brings the oxygen in the air of the lungs down to about 8 or 9 per cent. From this point onward the hyperpnea (augmented volume of breathing) increases progressively. Consciousness is lost when the inspired air (at normal barometric pressure) contains between 11 and 8 per cent of oxygen, but respiration is not abolished, and death is not quickly induced, until the percentage of oxygen has fallen several per cent lower. There are marked individual differences in the extent of decrease of oxygen pressure that can be endured, before fainting or unconsciousness occurs.

Perhaps the simplest illustration of the interaction of carbon dioxide and oxygen on breathing is afforded by such experiments as the following: A normal man usually finds that he can hold his breath for 30 to 50 seconds. If he inspires oxygen beforehand, a healthy athletic man may not be able to hold appreciably longer than before, for his normal breathing and circulation fully cover his needs; but often a less healthy subject who is habitually a little short of oxygen is able to hold his breath distinctly longer with oxygen. If now forced breathing is performed for a few minutes, everyone, healthy or otherwise, finds that the breath can then be held for much longer, even for two or three minutes at a time, because the carbon dioxide in the blood has been decreased. What is even more significant is the fact that, if forced breathing has been carried on long and actively enough, the impulse for return of breathing, the so-called breaking point of breath-holding, occurs before the normal amount of carbon dioxide has reaccumulated. The impulse to renew breathing is due in this case partly to carbon dioxide and partly to the depletion of oxygen in the blood and lungs. This is shown by the fact that if at the end of forced breathing the lungs are filled with oxygen (most easily inhaled from a bag), the breath can be held for twice or three times as long as after mere forced breathing without oxygen. Thus after forced breathing and oxygen inhalation it may be held for six or eight or even ten minutes or more. The length of time that a man can hold his breath, without previous forced breathing or oxygen inhalation, depends upon and is a fairly good index of the "dilution ratio" at which his breathing is set by the amount of alkali in his blood.

Mountain Sickness and Acclimatization.

The effects of low barometric pressure at considerable altitudes above sea level, and the condition known as mountain sickness, are fundamentally due to deficiency of oxygen. (They will be more fully discussed in the next chapter.) Persons residing permanently at a considerable altitude above sea level become acclimatized to that altitude. They constantly breathe a larger volume of air per unit

mass carbon dioxide eliminated than they would at sea level; in other words the alveolar carbon dioxide is diluted to a lower partial pressure. The greater the altitude and the lower the oxygen pressure, the greater the resting volume of breathing and in consequence the lower the carbon dioxide percentage in the lungs. The mass of carbon dioxide produced at an altitude during rest or for an equal amount of work is the same as at sea level. Evidently the partial pressure of oxygen, in other words the barometer, for all altitudes to which a man can become acclimatized determines the alveolar carbon dioxide which his respiration attempts to maintain. The fundamental factor, therefore, in the regulation of breathing is the partial pressure of oxygen, but except under acute conditions such as those in the experiments above referred to, the adjustments to the oxygen pressure are very slow, requiring days or weeks, while the adjustments to alteration of the concentration of carbon dioxide in the lungs are immediate. (See also pages 51 and 99.)

We cannot discuss these matters effectively, however, until we have considered the modes in which oxygen and carbon dioxide are carried in the blood.

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Chapter III.

Respiratory Functions of the Blood and Their Laws.

The blood is the principal agent for the transportation of substances from one part of the body to another. Of all the substances transported oxygen and carbon dioxide are the most immediately important. The volumes of these gases taken up and given off in the lungs and tissues are large and variable. During bodily rest the quantities in a man are about 0.2 to 0.3 liter of each gas per minute; during work 1.0 to 2.0 liters per minute, and during intense exertion 3.0 to 4.0 liters.

Three Functions of Hemoglobin.

Both oxygen and carbon dioxide dissolve in the blood in accord with the law of Henry; but the amounts held in simple solution at the gas pressures prevailing in the lungs and tissues (3 volumes per cent of carbon dioxide and 0.4 volume per cent of oxygen) are too small to afford an effective mode of transportation. If the volumes depended merely upon the law of Henry, that is on solubility, the alterations of their pressures during work would have to be very large as compared with those during bodily rest; for it is the essence of that law that every increase of the volume of gas dissolved in a liquid involves a proportional increase of the partial pressure of the gas. In fact, however, large volumes are transported with slight difference of pressure.

It has long been known that it is the special function of hemoglobin, the red coloring matter of the blood, to combine with oxygen and thus to enable the blood to take up oxygen in the lungs and to give it off in the tissues; thus in the lungs it is oxidized and in the tissues it is partially reduced again. It has now come to be recognized also that hemoglobin plays an almost equally important part in the transportation of carbon dioxide, although in quite a different manner. The two functions are in fact performed by different atomic groups in the hemoglobin molecule. It is a common mistake, and very misleading, to think of hemoglobin as exchanging oxygen for carbon dioxide in the tissues and vice versa in the lungs. Actually the blood may transport maximum quantities of both gases at once. The mechanisms of

transportation are distinct; nevertheless they exert a considerable reciprocal influence upon each other.

Carbon dioxide does not itself combine with hemoglobin. Among the numerous and complex properties of hemoglobin it has the capacity to act as a weak acid. As such it is combined with the alkalies which are normally in slight excess in the blood. As the blood passes thru the tissues, the carbon dioxide which they produce reacts with this alkali-hemoglobin to form alkali bicarbonates; and it is in the form of sodium bicarbonate, and to a less extent of other alkali bicarbonates, that carbon dioxide is held and transported in the blood.

It is characteristic of the way things are managed in the living body that owing to these properties of hemoglobin the blood is enabled to transport large volumes of oxygen and carbon dioxide, not only with slight alterations of their partial pressures, but also with a correspondingly slight alteration of the balance of acid and alkali elements in the blood. Hemoglobin thus performs three functions: (1) it combines with oxygen and gives it up again readily; (2) it provides the alkali to allow the formation of alkali bicarbonate for the transportation of carbon dioxide; and (3) it takes up and gives off alkali so readily, being itself a very weak acid, that it maintains the acid-alkali balance, that is the hydrogen ion concentration, of the blood within narrow limits of variation.

Combination of Oxygen with Hemoglobin.

Hemoglobin forms apparently a true stoichiometrical chemical compound with oxygen, altho the union is loose. Hemoglobin is a complex compound protein with a very large molecule and contains iron. This iron passes readily from a less to a more oxidized form and back again; one atom of the iron combining with two atoms of oxygen. The controlling condition is the partial pressure of oxygen to which the blood is exposed and with which it is equilibrated. In blood containing the amount of hemoglobin within the limits of variation normal for healthy men, complete saturation of the hemoglobin with oxygen amounts to about 18 to 20 volumes of this gas per hundred volumes of blood. This is termed 100 per cent saturation. Arterial blood which is in gaseous equilibrium with the atmosphere of the lungs (about 100 mm. partial pressure of oxygen) is about 97 per cent saturated. The average mixed venous blood returning from the body to the lungs in vigorous men during rest has lost about four volumes per cent of oxygen and is therefore about 75 per cent saturated. During vigorous exercise with a large consumption of oxygen in the tissues, the degree of unsaturation in the venous blood may

increase to 60 per cent or more, which is the same thing as a saturation of 40 per cent or less.

If the percentage saturations and the partial pressures corresponding to them were directly proportional, a 74 or a 40 per cent saturation would indicate a partial pressure of nearly 74 mm. and 40 mm. respectively. Actually they correspond with partial pressures of about 43 mm. and 26 mm. respectively. In other words the oxyhemoglobin dissociation curve has a form which is neither a straight line nor a simple exponential expression. It has an S shape rising from zero pressure and zero content of oxygen slowly at first at pressures below 10 mm.; then more rapidly so that it reaches 20 per cent saturation

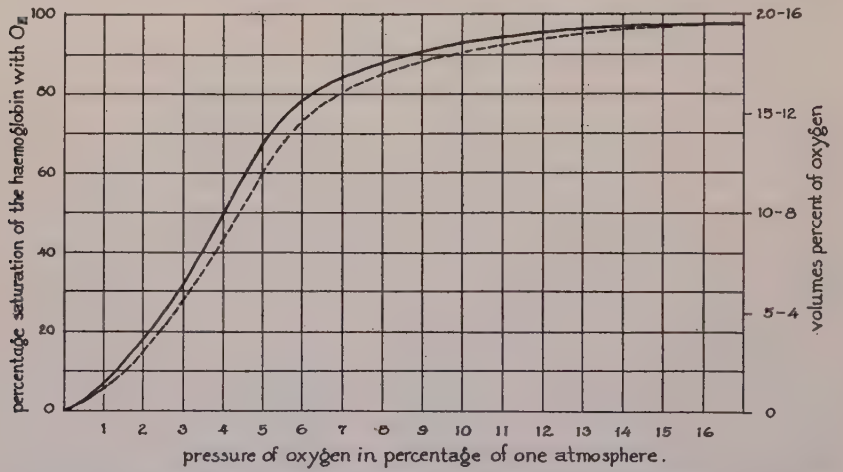

FIG. 2.—Oxyhemoglobin dissociation curve of blood in the presence of 40 mm. CO_2. Broken line, oxygen dissociation curve in the body.

at 15 mm.; 40 per cent at 26 mm.; 60 per cent at 35 mm.; 80 per cent at 48 mm.; and 97 per cent at 100 mm. From these figures and from the curve in figure 2 we can see at a glance why a slight lowering of the oxygen pressure in the air breathed and in that of the lungs (normally about 100 mm.) has a comparatively slight effect; for until the pressure is considerably reduced the amount of oxygen taken up by the blood is only slightly decreased.

The subject of the relations of oxygen and hemoglobin is extensive and complex and need not be pursued here. But it is important to note that the affinity of hemoglobin for oxygen is influenced by many factors, altho these factors, and their resultant general effect on hemoglobin, are held nearly constant during health. A pure or nearly pure solution of hemoglobin in water when equilibrated with various

pressures of oxygen affords a dissociation curve which is a rectangular hyperbola. At comparatively low oxygen pressures such a solution takes up, relatively to the amount of hemoglobin, much more oxygen than does hemoglobin under the conditions existing in blood. This oxyhemoglobin dissociation curve is markedly affected by the presence of salts (KCl, etc.) which cause it to take the S form above referred to. The dissociation curve is also especially sensitive to the hydrogen ion concentration of the fluid; even a slight increase in this condition causes a marked decrease, not in the total amount of oxygen held at complete saturation, but in the amount combined at any partial pressure corresponding to less than complete saturation, as shown by the lower curve in figure 2. In the blood hemoglobin is held in the corpuscles probably in a colloidal form. The concentration of the various salts is quite uniform and is kept at the normal values by the action of the kidneys.

Influence of Hydrogen Ion Concentration upon Hemoglobin.

The hydrogen ion concentration of the blood is nearly uniform, except that the increased carbon dioxide concentration of the venous blood induces a slight increase, which is immediately compensated by the elimination of carbon dioxide in the lungs. The coincident alterations of H-ion concentration act upon the dissociation of oxygen and hemoglobin, so that for a given content of oxygen the pressure is increased as the blood takes up carbon dioxide. Thus the giving off of oxygen in the tissues is effected at a distinctly higher pressure than would be the case without this action of carbon dioxide and of the H-ion concentration upon the affinity of hemoglobin for oxygen.

It may be seen from these facts why blood which has been hemolized, its corpuscles broken up by some toxic substance and the hemoglobin thrown into solution in the plasma of the blood, has properties which are distinctly abnormal. One of the writers has found, in illustration of this, that normal blood combines with oxygen and gives it off again with practically no heat of reaction, while he finds also (in common with others) that hemoglobin in solution has a distinct heat of reaction for combination with oxygen.

Transportation of Carbon Dioxide.

The dependence of the transportation of carbon dioxide upon hemoglobin, altho recognized in a general way many years ago by Zuntz and others, has only very recently been placed on a clear and complete basis. In normal blood, arterial and venous, carbon dioxide is not to any considerable extent combined with hemoglobin. In fact the greater part of it is not carried within the corpuscles, where all of

the hemoglobin normally is, but in the plasma or fluid of the blood. It is chiefly in the form of sodium bicarbonate, $NaHCO_3$.

Hemoglobin is none the less the essential agent; for plasma, when separated from its corpuscles and exposed to various pressures of carbon dioxide, takes up and gives off this gas in a manner which deviates comparatively little, and to that extent because of the buffer action of the plasma proteins, from a simple solution of this gas in water or salt solution in accord with the law of Henry. In the presence of corpuscles, however, the plasma and the blood as a whole show a dissociation curve for carbon dioxide which rises so far above mere solution that it enables the blood to transport comparatively large quantities of carbon dioxide under comparatively slight differences of pressure at the terminals in the tissues and lungs.

The hemoglobin molecule probably contains both acid and basic carboxyl and amido groups, and is therefore an amphoteric electrolyte. Its iso-electric point lies at a hydrogen ion concentration a little above, that is more acid than, that of blood, whose pH is 7.35. It therefore acts as an acid which is less dissociated and weaker than carbonic acid. In arterial blood the hemoglobin is largely combined with base, chiefly potassium, and potassium chloride is the principal salt in the corpuscles. The principal inorganic constituents in the plasma on the contrary are sodium chloride, 0.12 mol, and sodium bicarbonate, 0.02 mol.

The walls of the red corpuscles are nearly impermeable to kations, but fairly freely permeable to anions such as chlorine and HCO_3. Suppose now that arterial blood, whose plasma has the salt composition just stated, passes thru an active muscle where, owing to the higher pressure of carbon dioxide, it takes up a normal load of this substance. In solution carbon dioxide acts as carbonic acid, H_2CO_3; and depending upon the concentration of this carbonic acid, a redistribution of acids and bases occurs. Chlorine from sodium chloride passes into the corpuscles and combines with the potassium previously united to hemoglobin. The sodium thus liberated from sodium chloride in the plasma forms $NaHCO_3$. Within the corpuscles also carbon dioxide, or rather H_2CO_3, probably form $KHCO_3$ in analogous fashion, for the increase of carbon dioxide is usually distributed fairly equally between corpuscles and plasma, volume for volume. The plasma is, however, the larger volume and is therefore the principal medium of transportation. But it is the hemoglobin of the corpuscles which chiefly enables it to perform this function, although the proteins of plasma play a similar but much smaller rôle.

The distribution and redistribution of the various ions between the corpuscles and plasma which occur as the blood passes thru the lungs and thru the tissues, losing a little carbon dioxide in the one

and gaining a little in the other, seem to accord closely with the requirements of the theory of equilibrium across a semi-permeable membrane as formulated by Donnan. This is a field in which investigation is now active. The main outlines of the system chemically considered are thus fairly clear, while the details are complex. The foregoing discussion, therefore, emphasizes only those factors which bear upon the volume of breathing. Mention should, however, be made here of a chemical effect which seems to contribute an element characteristically physiological to the sum total of these reactions and processes. This consists in the fact demonstrated by Haldane that hemoglobin, when combined with oxygen, has distinctly stronger acid properties and is more dissociated in respect to the hydrogen of its carboxyl groups than when deoxygenated. Thus in the lungs the oxygenation of hemoglobin assists in displacing carbon dioxide from the blood, and in the tissues the loss of oxygen in itself renders the blood slightly more alkaline and thus better capable of taking up carbon dioxide. Recent observations by Van Slyke indicate that the giving off of ten parts of oxygen and the simultaneous taking up of seven parts of carbon dioxide leave the hydrogen-ion concentration of the blood unaltered. As the respiratory quotient is usually about 0.8 it is evident that, as Haldane was the first to show, the hydrogen-ion concentration of venous blood is only slightly higher than that of arterial blood.

Hydrogen-Ion Concentration of Blood.

In the chemistry of blood, as in all modern chemical thought, the conception of equilibrium is fundamental. A condition such as acidity or alkalinity is defined as an equilibrium and is measured by a figure indicating the amount of some element in a certain state when the atomic rearrangements due to the addition of some substance, such as an acid or alkali, are complete. Thus all possible degrees both of alkalinity and acidity are now expressed in terms of the number of hydrogen atoms or ions dissociated from water in the presence of acids or alkalies. In all watery solutions a minute part of the water exists thus dissociated; and the product of the $H \times OH$ ions is constant alike in pure water, neutral solutions of salts, and in acid and alkaline solutions of all strengths. Acids or alkalies influence this condition in proportion to their concentrations and to the degree of their dissociation; a weak acid, being less dissociated and maintaining fewer H ions is, therefore, weaker than strong acids. Dissociated alkalies similarly maintain more OH ions in the solution and reduce the H ions correspondingly.

The expression generally employed to indicate the H-ion concentra-

tion or C_H is unfortunately and unnecessarily complex and recondite; it is pH, which is the negative logarithm of the number of H ions in one cubic centimeter of the solution. As the pH figure increases the acidity and C_H decrease; pH equalling seven is neutrality. Both H and OH ions are then present in the amounts 1×10^{-7} in the fluid and being equal they balance as in water and afford neutrality.

By the hydrogen-ion concentration of blood is generally meant that of the plasma when the blood has a normal content of gases. It has been shown to depend with remarkable precision upon the simple relation first formulated by L. J. Henderson:

$$C_H = K \times \frac{H_2CO_3}{NaHCO_3} \qquad (1)$$

In this expression K is a constant identical apparently for all conditions of the plasma of all bloods. For all purposes here concerned we may therefore omit K and use the sign $\propto$, meaning proportional. Thus the concentration of H ions is proportional to the ratio of dissolved carbon dioxide to the alkali or combined carbon dioxide.

$$C_H \propto \frac{H_2CO_3}{NaHCO_3} \qquad (2)$$

The H_2CO_3 in the numerator of the fraction and in the ratio is simply the amount of carbon dioxide held in solution in the plasma according to the law of Henry. It varies always in direct proportion to the partial pressure of carbon dioxide. In other words it is the alveolar pressure of carbon dioxide multiplied by the constant for the solubility of carbon dioxide in blood at body temperature.

The $NaHCO_3$ of plasma which forms the denominator of the fraction is usually termed the alkaline reserve. The term is, however, unfortunate, for the real alkaline reserve of the blood is the hemoglobin, or potassium salt of hemoglobin, in the corpuscles. Thus if the corpuscles are separated from the plasma by centrifuging, the plasma may be neutralized by means of dilute hydrochloric acid very much as if it were a solution of sodium bicarbonate. But if the corpuscles are present and the blood is in an atmosphere of air plus 5 or 6 per cent carbon dioxide, enormously more hydrochloric acid is required to neutralize it. Whole blood has a far greater power than mere plasma to neutralize acid and to maintain approximate neutrality. The reason appears from the fact that if separated corpuscles are suspended in dilute neutral sodium chloride solution and exposed to an atmosphere of carbon dioxide and again centrifuged, a considerable part of the sodium is now found in the saline solution as bicarbonate. The chlorine ions have passed into the corpuscles and combined with potassium

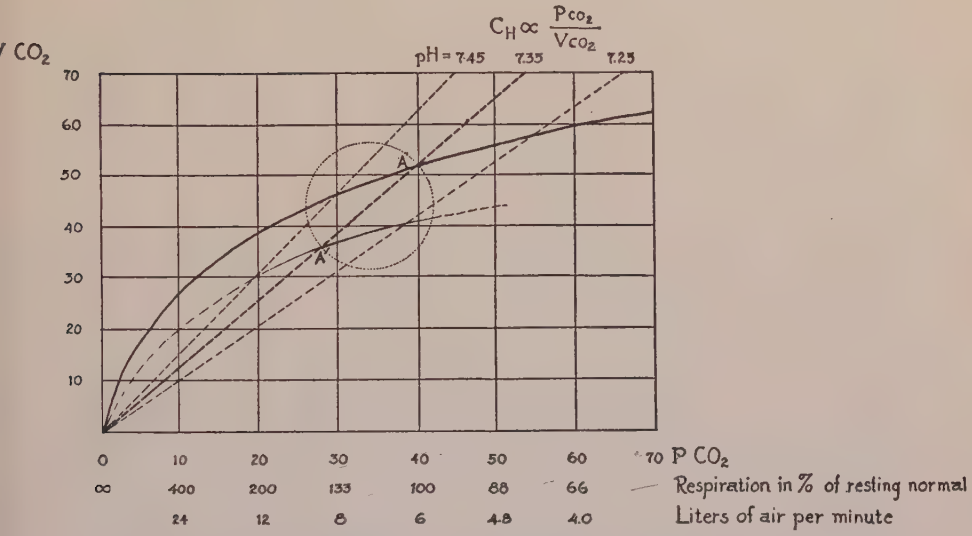

FIG. 3.—*The CO_2 Diagram.* The point marked A indicates the condition of the arterial blood. It lies upon the CO_2 dissociation curve, the solid line, which expresses by the scale at the left the alkali available in the blood, its CO_2 combining power at the time. The point on the curve at which A is held is determined by the pressure of CO_2, according to the scale immediately below the abscissa. In the next scale below are given the volumes of breathing, and below that the number of liters of air per minute in the breathing, which would give each particular pressure of CO_2 and would hold the arterial blood, A, at corresponding points to the right or left on the dissociation curve. The mass of CO_2 produced is assumed to be constant.

The oblique lines express the H-ion concentration for the points at which each intersects the dissociation curve. Each line expresses a certain relation of $P_{CO_2} : V_{CO_2}$ and therefore a constant H-ion concentration thruout its length.

If the volume of breathing, here indicated as six liters per minute, is increased to eight, because of a slight oxygen deficiency due to prolonged breathing of some asphyxiant, the A point is thereby shifted to the left. The blood is then abnormally alkaline; and as a compensation alkali passes out of the blood, and the dissociation curve is lowered, until the new arterial point A′ lies at the intersection of a new and lower dissociation curve and the normal H-ion diagonal. When, on the other hand, excess of oxygen is supplied, the breathing is gradually depressed; the A point moves to the right—and even more rapidly under inhalation of oxygen plus CO_2—and the blood is therefore abnormally rich in carbonic acid, and its H-ion concentration abnormally high. In compensation of this condition more alkali is called into the blood, and the dissociation curve is thus restored to a normal level. The dotted circle along which the A point moves counterclockwise indicates the course of such readjustments of the level of the CO_2 dissociation curve, under the influence of variations in the supply of oxygen and other fundamental conditions. The diagram as a whole shows how the volume of breathing, the amount of alkali in use in the blood, and the H-ion concentration interact to achieve normal relations.

previously held by hemoglobin. This process of bicarbonate production may be repeated by transferring the corpuscles to fresh saline, until a total of 200 or 300 volumes per cent of combined carbon dioxide or $NaHCO_3$ is thus produced. (The volume of the original blood, from which the corpuscles were obtained, is taken as 100.) In figure 3 is reproduced the CO_2 diagram devised by the authors to show these relations.

Fundamental Factors Regulating Respiration.

With these features of the blood as a physico-chemical system before us we may now describe more precisely than was possible in the previous chapter the physiological regulation of breathing. There are three controls of respiration: the immediate, the intermediate, and the fundamental. (1) The immediate control is exercised by the amount of carbon dioxide which the body produces and eliminates at the time. (2) The intermediate control is effected by the blood alkali which, in proportion to its amount, holds the dilution ratio of breathing at some nearly constant figure for the liters of air breathed per liter of carbon dioxide exhaled. It does this thru the sensitiveness of the respiratory center to the H-ion concentration of the blood. (3) The fundamental control is the oxygen pressure to which the individual is acclimatized. It determines, or on change of altitude (or barometric pressure) it readjusts, the amount of the blood alkali. It accomplishes this thru the depressant influence on respiration exerted by each increase of oxygen pressure, or by the slowly developing stimulation of breathing which results from decrease of oxygen. This depression of breathing renders the blood relatively acid by accumulation of carbonic acid. On the other hand the stimulation of breathing by low oxygen causes slight overbreathing with depletion of carbonic acid, and consequently a relatively too alkaline blood. In the normal body depressed breathing and acidosis (the only condition properly so-called outside of acute disease) tend to draw alkali into the blood from some undefined source. This process for increasing the blood alkali is used by the system in a manner characteristic of the purposefulness of biological mechanisms. Alkalosis, a low ratio of $H_2CO_3 : NaHCO_3$, no matter whether the blood alkali be absolutely high or low, is utilized by the organism to reduce the blood alkali, partly thru the urine and partly in still undefined ways.

These controls and processes of recovering equilibrium, or seeking to recover it, for the process is more or less ineffective in some intoxications and in pathological conditions mistakenly termed "uncompensated acidosis," will now be defined as precisely as present knowledge permits.

While there is some evidence that carbon dioxide exerts a specific influence upon the respiratory center, probably because of its high diffusibility thru tissues, it is as well established as any fact in physiology that in general it is thru the part which carbon dioxide plays in determining the H-ion concentration of the blood that it influences the respiratory center. This (in view of equation 2 given above) is equivalent to saying that respiration is regulated by the relation of the amounts of the dissolved carbon dioxide, H_2CO_3, and the combined carbon dioxide, $NaHCO_3$, in the plasma. Thus any increase of carbonic acid tends to increase respiration, while on the contrary any increase of the combined carbon dioxide or bicarbonate tends to decrease it; but it is their ratio, not their sum or difference, which regulates.

Laws of the Hemato-Respiratory Functions.

I. Control by Alveolar Carbon Dioxide. The minute to minute variations in the volume of breathing are due almost wholly to the dissolved carbonic acid; the blood alkali holding nearly constant and therefore playing practically no part in the variations. They are caused as follows: The variations in the amount of carbon dioxide produced in the body caused alterations of pressure of carbon dioxide; and this pressure increases or decreases the amount dissolved and determines the carbonic acid, H_2CO_3, in the blood. The H-ion concentration is altered in the same direction; but respiration responds almost instantly, and in consequence the alterations are so slight as to be scarcely detectable by any method now available. Thus the first law is: The volume of pulmonary ventilation varies almost exactly in proportion to the carbon dioxide production of the body and thus holds the pressure of carbon dioxide in the air of the lungs nearly uniform. The law may be expressed in the roughly mathematical form:

$$\text{Pulmonary ventilation} = CO_2 \text{ produced} \times \frac{100}{\text{alveolar } CO_2 \text{ pressure}}. \quad (3)$$

In this expression the pulmonary ventilation and carbon dioxide production are the variables and are measured in cubic centimeters or liters per minute, while the alveolar carbon dioxide pressure is measured in per cent of an atmosphere and is regarded as a constant.

II. Control by Blood Alkali. The second of the modes of regulation of breathing depends wholly upon the blood alkali or combined carbon dioxide, $NaHCO_3$. The greater the amount of this factor the less the volume of breathing. Evidently the ion HCO_3, the form in which carbon dioxide chiefly exists in blood, is not a stimulant, but rather a depressant of breathing. This regulation has, however,

no immediate relation to the minute to minute variations of breathing. It is the dilution factor, previously referred to, which sets the volume of breathing per unit mass of carbon dioxide produced. It determines, therefore, whether the alveolar carbon dioxide pressure of the individual at the time is 3, 4, 5, or 6 per cent of an atmosphere or less or more. Any given amount of $NaHCO_3$ in the plasma, such as 30 or 40 or 50 or more units (measured as volumes per cent of combined carbon dioxide), requires a proportional amount of H_2CO_3 to be held in simple solution in order to produce the H-ion concentration which is normal in healthy blood (since the H ions are proportional to the ratio $H_2CO_3 : NaHCO_3$). The partial pressure of carbon dioxide which respiration is required to maintain in the lungs when the blood alkali is 40 must therefore be four-fifths of that when the alkali is 50, or four-sixths of that when it is 60.

Thus whatever the amount of the blood alkali may be, the alveolar pressure of carbon dioxide must bear a proportional relation to it in order to keep the ratio $H_2CO_3 : NaHCO_3$ uniform and normal. As we have already shown, the volume of breathing per unit mass of carbon dioxide produced must, by the principle of dilution, vary in inverse proportion to the alveolar pressure of carbon dioxide maintained. Thus when the alveolar carbon dioxide is 5 per cent of an atmosphere the dilution factor is 20 (since $5 \times 20 = 100$), and if it were 4 per cent the factor would be 25. A low, or greatly diluted, alveolar carbon dioxide requires therefore a large volume of air; and a high, or slightly diluted, alveolar carbon dioxide requires for the same mass of carbon dioxide only a comparatively small amount of air. Thus to put the point in roughly mathematical form:

Since from equation (3) above

$$\text{Alveolar } CO_2 \text{ pressure} = \frac{CO_2 \text{ production}}{\text{Pulmonary ventilation}}; \qquad (4)$$

and since the carbon dioxide dissolved in blood plasma varies with the partial pressure of carbon dioxide, that is,

$$H_2CO_3 = \text{Alveolar } CO_2 \text{ pressure} \times \text{constant}; \qquad (5)$$

and since respiration adjusts the relations of the dissolved to the combined carbon dioxide, so that

$$\frac{H_2CO_3}{NaHCO_3} = \frac{\text{H-ions}}{\text{a constant}} = \text{uniform H-ion concentration}: \qquad (6)$$

therefore

$$\text{Pulmonary ventilation} = \frac{CO_2 \text{ produced} \times \text{constant}}{NaHCO_3}. \qquad (7)$$

The second law is: The amount of the blood alkali determines, by inverse proportion, the adjustment or dilution ratio of the volume of the pulmonary ventilation per unit mass of carbon dioxide produced at which the respiration of the individual at the time is set.

It follows as a practical consequence of this law that an analysis of the alveolar carbon dioxide pressure and an analysis of the alkaline reserve of the blood afford almost exactly the same information and in only slightly different terms.

III. Interfactorial Control of Equilibrium. The values for the arterial oxygen and CO_2 pressures, and for the amount of blood alkali have very nearly the same proportion to each other at all altitudes, while the volume of breathing per unit mass carbon dioxide produced varies inversely to the other quantities. This is the third law. Thus, if K_1, K_2, K_3, K_4, are constants with the values respectively of 100 mm., 50 volumes per cent, 40 mm. and a dilution factor 18, these being normal sea level values, the law for all oxygen pressures may be formulated thus:

$$\frac{\text{Oxygen pressure in lung air}}{K_1} = \frac{\text{Blood alkali}}{K_2} = \frac{\text{Alveolar } CO_2 \text{ pressure}}{K_3} = \frac{K_4}{\text{Pulmonary ventilation per unit mass } CO_2 \text{ eliminated}} \quad (8)$$

At sea level each member of this equation comes to $\frac{1}{1}$; on the shoulder of Mount Everest each would be about $\frac{1}{2}$.

IV. Control of pH by Oxygen. This relation is defined by the fourth law, as follows: Whenever the partial pressure of oxygen in the arterial blood (expressed in millimeters) is above the ratio 100 : 50, as compared with the alkali (expressed in volumes per cent combined carbon dioxide) respiration is depressed, relatively to the blood alkali, so that the ratio $H_2CO_3 : NaHCO_3$, and presumably the H-ion concentration, are raised above normal (low pH). Whenever the oxygen-alkali ratio falls below 100 : 50, respiration is stimulated, relatively to the blood alkali. Thus the ratio $H_2CO_3 : NaHCO_3$, and presumably the H-ion concentration, are decreased (high pH).

V. Control of Blood Alkali by pH. Whenever a depression of breathing forces and holds the ratio $H_2CO_3 : NaHCO_3$ above normal, causing a low pH, an increase of blood alkali tends to occur. Whenever overbreathing holds the ratio below normal, causing a high pH, alkali tends to pass out of the blood. Both processes tend thus to bring the

ratio back to normal and to restore a normal pH at a new level of alkali. If the arrow signifies "leads to," this fifth law may be expressed thus:

(Oxygen: $[H\overline{CO_3}] > 100:50$) → Depressed breathing → $\frac{H_2CO_3}{NaHCO_3}$ (above normal) → increase of alkali and thus compensated pH with a higher blood alkali. (9)

(Oxygen: $[H\overline{CO_3}] < 100:50$) → Overbreathing → $\frac{H_2CO_3}{NaHCO_3}$ (below normal) → decrease of alkali and thus compensated pH with a lower blood alkali. (10)

This means that the immediate cause of low pH is always a relative depression of breathing, and that the purpose of low pH is to call more alkali into the blood; while the immediate cause of high pH is always overbreathing and its purpose is to drive some of the alkali out of the blood.

Principle of Physiological Regulation.

The readjustments which the body makes to variations in the environmental conditions and particularly the functions which hemoglobin fulfills in regard to oxygen, carbon dioxide and H ions in the blood afford an illustration of the principle, which is basic in physiology, that the living system is organized so that, in spite of wide variations in activity and in external conditions, the internal conditions which constitute health, such as the gas pressures, hydrogen-ion concentration, osmotic pressure and other physiological constants, are maintained nearly uniform. In part this approximate constancy, or narrow variation around a mean value, is provided for by means of buffers, mechanical and chemical, such as the large volume of stationary air in the lungs, and the amphoteric proteins and the sodium bicarbonate of the blood. But fundamentally the regulation of the constants of the body, and the maintenance of health, is a quality of life which lies beyond the capacity of the physics and chemistry of today to explain. It is the quality termed φυσις, or physis (from which physiology takes its name); the "something working toward an end," the self-repairing and recovering power, which is scarcely if at all perceptible in ordinary mechanisms, such as steam engines and automobiles. Amid the successes which have crowned

the application of chemistry to biological problems, it is often, but should not be, forgotten that physiological equilibrium is something very much more than merely the various equilibria of chemistry. An organism does indeed operate chemically, as in the blood. But the equilibrium of a man or animal is alive in the sense of being dynamic and actually restorative in innumerable functions, as yet only dimly understood, just as the processes of hunger and thirst and the actions to which they lead make good the expenditures of energy and water. So, as we see them in the blood, the respiratory functions are not to be understood as a mere chemical equilibrium. In the presence of a high oxygen pressure respiration depresses itself, so to speak, and allows carbon dioxide to accumulate up to a relatively high H-ion concentration, and this induces a rapid counterbalancing increase of alkali which brings the H-ion concentration back to normal. When the pressure or amount of oxygen in the blood is reduced, as when a man goes from sea level up to some higher altitude and lives there, or when he works continually in an atmosphere containing a small amount of carbon monoxide, respiration is stimulated, the partial pressure of carbon dioxide is decreased, alkali passes out of the blood to a corresponding extent and acclimatization to the particular altitude or contaminated atmosphere results. But a strain is involved, and altho acclimatization may become nearly complete if the condition inciting it is maintained, a condition similar to the overtraining or "staleness" of an athlete may develop in aviators and in persons exposed to carbon monoxide intermittently.

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Chapter IV.

Practical Applications of the Laws of Gases and Vapors.

The laws defining the behavior of gases are among the simplest of the principles of science, and their formulas are easily learned. The mistakes, to which nearly everyone is liable in applying them to any but familiar types of problems, are equally simple and easy to make. What, for instance, is the lifting power of helium as compared with hydrogen in a balloon? (Molecular weights, 4 and 2 respectively). Two of the most eminent of American scientists replied offhand: "One-half." The correct answer is, of course, "approximately twenty-four twenty-sixths, if we take air at a mean molecular weight of twenty-eight."

Similarly in respect to negative pressures the correct conception does not always come first. Suppose one side of the thorax has been punctured and the lung on that side has collapsed. (See figure 1, page 22.) Will the heart, which with its connections forms a slightly flexible partition dividing the chest into two compartments, be pressed toward or away from the intact lung? And suppose an inspiration is drawn so that the intact lung is inflated further, will the heart be pressed more or less firmly in that direction? "Toward the intact lung," and "more firmly," are the mechanically correct answers, although the opposite answers are frequently given offhand. For an anatomical reason the heart is moved by inspiration toward the deflated lung, but the usual reason offered for the answer arises from a misapprehension of the mechanics of the chest. The way in which the lung is expanded by a negative pressure on its pleural surface prevents its ever pushing against the heart.

A third common mistake occurs in calculating the respiratory quotient (see page 27). It is natural to divide the per cent of carbon dioxide in the expired air by the apparent oxygen deficit in the air, that is by the figure by which its oxygen content falls short of 20.93 per cent. But this overlooks the fact that the volume of the expired air at all respiratory quotients below 1.0 is less than that of the inspired air, and thus leads to an error which is sometimes important. It is corrected by use of the fact (or assumption) that the volumes of nitrogen

in the inspired and expired airs are exactly the same. Many problems in this field present themselves, like these three examples, as elementary but tricky puzzles.

The laws of Boyle, Charles, and Henry, and the strict statement of the behavior of vapors may be found in textbooks of physics and need not be repeated here. But an attempt will be made in this chapter to show the kind of use to which these fundamental principles are put in the field of respiration, and some of the easy and frequent mistakes that are prone to occur. No attempt will be made at rigorously exact definitions or rules, but rather to place warnings near the various false turnings of the paths in this field. The important thing is to develop the instinct for seeing each problem from a correct and practical angle.

Modes of Expressing Concentration of Gas.

There are commonly in use four forms of expression for the concentration of gases or vapors in air: (1) per cent by volume, (2) parts by volume, (3) partial pressure, and (4) weight per volume (milligrams per liter) of air. Each has advantages for particular circumstances and is convertible into any of the other forms.

Partial pressure and per cent by volume are generally employed to express the concentration of the common respiratory gases, oxygen, nitrogen, and carbon dioxide, and for the relatively inert gases, such as methane and hydrogen, which must be present in high concentration to be of importance to life.

The form parts by volume, or parts per thousand, per ten thousand, or per million parts of air, is employed to give the concentration of more actively toxic gases. Recently in this country the form "parts per million" has been generally adopted. This mode of expression is convenient in many cases, but it does not afford a true basis of comparison of the toxicity of the various volatile substances, except when they have nearly the same molecular weight. For instance, to compare the toxicity of equal volumes of ammonia gas (molecular weight 17) and of bromine vapor (molecular weight 80) would be quite misleading, for one would contain by weight nearly five times as much of the active substance per unit volume of air respired as the other.

The expression of concentration by the weight of the volatile substance per unit volume of air, usually as milligrams per liter, affords not only a ready means of comparison of the toxicity of the various gases and vapors but also the best basis for estimating the rate at which air is vitiated by vapor from a volatilizing fluid, and the rate at which a gas or vapor is absorbed in the lungs. A table for conversion of concentrations from parts by volume to milligrams per liter and vice versa is here quoted.

Conversion Table for Gases: Parts per Million Versus Milligrams per Liter.[1]

[25° C. and 760 mm. mercury, barometric pressure.]

Molecular Weight	1 Mg./L.-p.p.m.	1 p.p.m.-Mg./L.	Molecular Weight	1 Mg./L.-p.p.m.	1 p.p.m.-Mg./L.	Molecular Weight	1 Mg./L.-p.p.m.	1 p.p.m.-Mg./L.
1.....	24,450	0.0000409	51.....	479	0.002086	101.....	242.1	0.00413
2.....	12,230	.0000818	52.....	470	.002127	102.....	239.7	.00417
3.....	8,150	.0001227	53.....	461	.002168	103.....	237.4	.00421
4.....	6,113	.0001636	54.....	453	.002209	104.....	235.1	.00425
5.....	4,890	.0002045	55.....	445	.002250	105.....	232.9	.00429
6.....	4,075	.0002454	56.....	437	.002290	106.....	230.7	.00434
7.....	3,493	.0002863	57.....	429	.002331	107.....	228.5	.00438
8.....	3,056	.000327	58.....	422	.002372	108.....	226.4	.00442
9.....	2,717	.000368	59.....	414	.002413	109.....	224.3	.00446
10.....	2,445	.000409	60.....	408	.002554	110.....	222.3	.00450
11.....	2,223	.000450	61.....	401	.002495	111.....	**220.3**	.00454
12.....	2,038	.000491	62.....	394	.00254	112.....	**218.3**	.00458
13.....	1,881	.000532	63.....	388	.00258	113.....	216.4	.00462
14.....	1,746	.000573	64.....	382	.00262	114.....	214.5	.00466
15.....	1,630	.000614	65.....	376	.00266	115.....	212.6	.00470
16.....	1,528	.000654	66.....	370	.00270	116.....	210.8	.00474
17.....	1,438	.000695	67.....	365	.00274	117.....	209.0	.00479
18.....	1,358	.000736	68.....	360	.00278	118.....	207.2	.00483
19.....	1,287	.000777	69.....	354	.00282	119.....	205.5	.00487
20.....	1,223	.000818	70.....	349	.00286	120.....	203.8	.00491
21.....	1,164	.000859	71.....	344	.00290	121.....	202.1	.00495
22.....	1,111	.000900	72.....	340	.00294	122.....	200.4	.00499
23.....	1,063	.000941	73.....	335	.00299	123.....	198.8	.00503
24.....	1,019	.000982	74.....	330	.00303	124.....	197.2	.00507
25.....	978	.001022	75.....	326	.00307	125.....	195.6	.00511
26.....	940	.001063	76.....	322	.00311	126.....	194.0	.00515
27.....	906	.001104	77.....	318	.00315	127.....	192.5	.00519
28.....	873	.001145	78.....	313	.00319	128.....	191.0	.00524
29.....	843	.001186	79.....	309	.00323	129.....	189.5	.00528
30.....	815	.001227	80.....	306	.00327	130.....	188.1	.00532
31.....	789	.001268	81.....	302	.00331	131.....	186.6	.00536
32.....	764	.001309	82.....	298	.00335	132.....	185.2	.00540
33.....	741	.001350	83.....	295	.00339	133.....	183.8	.00544
34.....	719	.001391	84.....	291	.00344	134.....	182.5	.00548
35.....	699	.001432	85.....	288	.00348	135.....	181.1	.00552
36.....	679	.001472	86.....	284	.00352	136.....	179.8	.00556
37.....	661	.001513	87.....	281	.00356	137.....	178.5	.00560
38.....	643	.001554	88.....	278	.00360	138.....	177.2	.00564
39.....	627	.001595	89.....	275	.00364	139.....	175.9	.00569
40.....	611	.001636	90.....	272	.00368	140.....	174.6	.00573
41.....	596	.001677	91.....	269	.00372	141.....	173.4	.00577
42.....	582	.001718	92.....	266	.00376	142.....	172.2	.00581
43.....	569	.001759	93.....	263	.00380	143.....	171.0	.00585
44.....	556	.001800	94.....	260	.00384	144.....	169.8	.00589
45.....	543	.001840	95.....	257	.00389	145.....	168.6	.00593
46.....	532	.001881	96.....	255	.00393	146.....	167.5	.00597
47.....	520	.001922	97.....	252	.00397	147.....	166.3	.00601
48.....	509	.001963	98.....	249.5	.00401	148.....	165.2	.00605
49.....	499	.002004	99.....	247.0	.00405	149.....	164.1	.00609
50.....	489	.002045	100.....	244.5	.00409	150.....	163.0	.00613

Factors for conversion of some units.

1. Mg. per L. × 28.32 = Mg. per cu. ft.
2. Mg. per L. × 1,000 = Mg. per cu. m.
3. Mg. per cu. ft. × 35.314 = Mg. per cu. m.
4. Mg. per cu. meter × 0.02832 = Mg. per cu. ft.

[1] U. S. Bureau of Mines, Technical Paper 248 (1921).

Molecular Weight	1 Mg./L.-p.p.m.	1 p.p.m.-Mg./L.	Molecular Weight	1 Mg./L.-p.p.m.	1 p.p.m.-Mg./L.	Molecular Weight	1 Mg./L.-p.p.m.	1 p.p.m.-Mg./L.
151.....	161.9	0.00618	201.....	121.6	0.00822	251.....	97.4	0.01027
152.....	160.9	.00622	202.....	121.0	.00826	252.....	97.0	.01031
153.....	159.8	.00626	203.....	120.4	.00830	253.....	96.6	.01035
154.....	158.8	.00630	204.....	119.9	.00834	254.....	96.3	.01039
155.....	157.7	.00634	205.....	119.3	.00838	255.....	95.9	.01043
156.....	156.7	.00638	206.....	118.7	.00843	256.....	95.5	.01047
157.....	155.7	.00642	207.....	118.1	.00847	257.....	95.1	.01051
158.....	154.7	.00646	208.....	117.5	.00851	258.....	94.8	.01055
159.....	153.7	.00650	209.....	117.0	.00855	259.....	94.4	.01059
160.....	152.8	.00654	210.....	116.4	.00859	260.....	94.0	.01063
161.....	151.9	.00658	211.....	115.9	.00863	261.....	93.7	.01067
162.....	150.9	.00663	212.....	115.3	.00867	262.....	93.3	.01072
163.....	150.0	.00667	213.....	114.8	.00871	263.....	93.0	.01076
164.....	149.1	.00671	214.....	114.3	.00875	264.....	92.6	.01080
165.....	148.2	.00675	215.....	113.7	.00879	265.....	92.3	.01084
166.....	147.3	.00679	216.....	113.2	.00883	266.....	91.9	.01088
167.....	146.4	.00683	217.....	112.7	.00888	267.....	91.6	.01092
168.....	145.5	.00687	218.....	112.2	.00892	268.....	91.2	.01096
169.....	144.7	.00691	219.....	111.6	.00896	269.....	90.9	.01100
170.....	143.8	.00695	220.....	111.1	.00900	270.....	90.6	.01104
171.....	143.0	.00699	221.....	110.6	.00904	271.....	90.2	.01108
172.....	142.2	.00703	222.....	110.1	.00908	272.....	89.9	.01112
173.....	141.3	.00708	223.....	109.6	.00912	273.....	89.6	.01117
174.....	140.5	.00712	224.....	109.2	.00916	274.....	89.2	.01121
175.....	139.7	.00716	225.....	108.7	.00920	275.....	88.9	.01125
176.....	138.9	.00720	226.....	108.2	.00924	276.....	88.6	.01129
177.....	138.1	.00724	227.....	107.7	.00928	277.....	88.3	.01133
178.....	137.4	.00728	228.....	107.2	.00933	278.....	87.9	.01137
179.....	136.6	.00732	229.....	106.8	.00937	279.....	87.6	.01141
180.....	135.8	.00736	230.....	106.3	.00941	280.....	87.3	.01145
181.....	135.1	.00740	231.....	105.8	.00945	281.....	87.0	.01149
182.....	134.3	.00744	232.....	105.4	.00949	282.....	86.7	.01153
183.....	133.6	.00748	233.....	104.9	.00953	283.....	86.4	.01157
184.....	132.9	.00753	234.....	104.5	.00957	284.....	86.1	.01162
185.....	132.2	.00757	235.....	104.0	.00961	285.....	85.8	.01166
186.....	131.5	.00761	236.....	103.6	.00965	286.....	85.5	.01170
187.....	130.7	.00765	237.....	103.2	.00969	287.....	85.2	.01174
188.....	130.1	.00769	238.....	102.7	.00973	288.....	84.9	.01178
189.....	129.4	.00773	239.....	102.3	.00978	289.....	84.6	.01182
190.....	128.7	.00777	240.....	101.9	.00982	290.....	84.3	.01186
191.....	128.0	.00781	241.....	101.5	.00986	291.....	84.0	.01190
192.....	127.3	.00785	242.....	101.0	.00990	292.....	83.7	.01194
193.....	126.7	.00789	243.....	100.6	.00994	293.....	83.4	.01198
194.....	126.0	.00793	244.....	100.2	.00998	294.....	83.2	.01202
195.....	125.4	.00798	245.....	99.8	.01002	295.....	82.9	.01207
196.....	124.7	.00802	246.....	99.4	.01006	296.....	82.6	.01211
197.....	124.1	.00806	247.....	99.0	.01010	297.....	82.3	.01215
198.....	123.5	.00810	248.....	98.6	.01014	298.....	82.0	.01219
199.....	122.9	.00814	249.....	98.2	.01018	299.....	81.8	.01223
200.....	122.3	.00818	250.....	97.8	.01022	300.....	81.5	.01227

Weight of Gas Volumes.

One gram molecule of every gas occupies the same volume as one gram molecule of every other gas when measured under the same conditions of pressure and temperature. This means that equal volumes contain the same number of molecules and that the weights in grams are in the same relation as the molecular weights of the substances. At 0°C. and 760 mm. this volume is 22.4 liters. The weight of one liter of any gas at 0°C. and 760 mm. therefore is the gram molecular weight divided by 22.4. The molecular weight of oxygen is 32; the weight of one liter of oxygen under standard conditions is $\frac{32}{22.4}$ or 1.428 grams. At other temperatures and pressures the weight of one liter of oxygen is modified according to the laws of pressure and temperature, as given hereafter. Thus one liter of oxygen at 38°C., 740 mm. and wet (water vapor 50 mm.) will weigh:

$$1.428 \times \frac{(740 - 50) \times (273)}{760 \times (273 + 38)} = 1.138 \text{ grams.}$$

The weight of a unit volume is important in expressing the concentration of various gases in air. As stated above, the most convenient and precise mode of expression is in milligrams of the substance per liter of air. An expression of this type is readily converted into percentage or into parts (i.e. volumes) of the gas in question per million volumes of air. To make this conversion the number of milligrams of the substance per liter of air is divided by the molecular weight of the substance and then multiplied by 0.0224 to find the number of cubic centimeters of the gas in question per liter of air; one-tenth of the number of cubic centimeters is the percentage; a thousand times the number of the cubic centimeters per liter would be the parts per million.

Gage Pressure and Absolute Pressure.

The uses of gages for the measurement of gas or vapor pressures causes much confusion, when the requisite distinction between absolute pressure and gage pressure is disregarded. For work under compressed air, as in caissons and deep-sea diving, it is the absolute pressure which is the essential factor causing nitrogen to dissolve in the blood, and thus if the pressure is lowered too rapidly induces caisson disease. But in this and many other practical matters it is customary and convenient from an engineering standpoint to express values in terms of gage pressure. Gage pressure is the difference between two absolute pressures. The ordinary steam gage furnishes an illustration. With no fire under

the boiler and with free connections to the outside air the gage rests at zero pressure, altho the pressure within the boiler is actually one atmosphere or fifteen pounds on each square inch. Such also is the pressure surrounding the gage. On closing the boiler and firing it, the pressure recorded on the gage rises, let us say, to a reading of fifteen pounds. The pressure within is thus fifteen pounds greater than the outside pressure, while the absolute pressure within the boiler is thirty pounds. That the reading of the gage is purely relative is further illustrated by supposing the gage reversed and placed inside of the boiler with its steam connection opening outside of the boiler. Under this condition the pressure recorded will be below zero of the gage and each pound rise of steam will be read as a "pound of vacuum" in the surrounding air. The absurdity of this is at once apparent with a hundred pounds steam pressure in the boiler and a gage reading of the surrounding air showing a vacuum of 100 pounds—manifestly impossible, for an absolute vacuum is a negative pressure of only 15 pounds.

Altho we do not commonly think of air as exerting any pressure against the inside of a flask which contains it, it is in reality exerting an outward pressure equal to the inward pressure exerted by the weight of air pressing against the outside of the flask. But if the air is sucked out by means of a pump, and the outward propulsive force is thus removed the flask may be collapsed by the inward pressure of the air surrounding it. The barometer is the instrument employed to measure the weight of the surrounding air. It is calibrated on a scale of absolute pressure which has as its zero a complete vacuum. But in ordinary life and in many conditions of chemistry and engineering the zero referred to is atmospheric pressure. It is essential always to keep in mind which of these zeros is being used. At sea level the average absolute pressure of the surrounding air is 760 mm. of mercury; this varies slightly with the meteorological conditions, and widely with the altitude above sea level at which the measurement is made. The normal absolute pressure at Pike's Peak, Colorado (altitude 14,100 feet) is about 450 mm. of mercury. There is a decrease of approximately 22 mm. of mercury per thousand feet of elevation up to about 13,000 feet, after which the decrease is somewhat less rapid.

Misapprehension of the distinction between gage and absolute pressure is not limited to the field of gas measurement. A particularly striking example is the common belief that nosebleed among those going to high altitudes is the result of the decrease in the external pressure of the air. It is true that the blood pressure (gage pressure) is the same at high and low altitudes while the atmospheric pressure (absolute pressure) is decreased as we ascend. It is argued that the vessels are therefore under a greater strain and that the blood must

tend to escape. Reference to absolute pressure shows however that the absolute blood pressure has fallen by the exact amount that atmospheric pressure has decreased. The hemorrhage is in reality due to the drying and cracking of the nasal membrane as a result of the increased evaporation in the dry and rarefied air.

It might be thought that the pressure of the gases in the blood would play a part, for instance the pressure of nitrogen. There is indeed a pressure of nitrogen in the blood, but it soon comes to be equal to that of the nitrogen in the air breathed. The same amount of nitrogen is held in solution in venous as in arterial blood and therefore the pressure of nitrogen is the same in each. In like manner the fact that arterial blood pressure is usually 100 mm. of mercury higher than venous blood pressure does not at all affect the nitrogen pressure, nor does it make the pressures of oxygen or carbon dioxide at all higher in the arterial than in the venous blood. Gas pressures in the blood and blood pressure have no direct relations.

Relations of Volume and Pressure.

A gas is a substance existing in a low degree of aggregation and exhibits therefore a high degree of compressibility. The volume occupied by any mass of gas, the temperature remaining constant, is determined by the pressure exerted upon it. Furthermore, the change in volume is proportional to the change in absolute pressure, not the gage pressure. The volumes (V and V′) occupied by the same mass of gas at two pressures (P and P′) will therefore vary in the ratio $\frac{V}{V'} = \frac{P'}{P}$ or concretely for a given mass of gas expanded or compressed to a certain extent (say one-half) $\frac{1V}{2V} = \frac{2P}{1P}$. That is the pressure increases as the space occupied decreases and vice versa. In order to compare the amounts of gas in units of volume it is essential therefore that the pressures at which they are measured should be known; otherwise the comparison may be wholly misleading.

Partial Pressures.

The pressure exerted by a mixture of gases in a bag or other collapsible container is equal to the pressure exerted upon it and is the sum of all the pressures of the component gases. Each acts separately according to the principle just stated, and the pressure exerted by each is known as its partial pressure. To illustrate this, suppose all the air to be sucked out of a one liter flask; the pressure within the flask would then be zero. The pressure exerted upon the outside of the flask would be that of the prevailing barometer, B. Into this flask is now run an

amount of oxygen which, measured at the prevailing barometer, would be half a liter. A pressure reading shows that the pressure within the flask is $\frac{B}{2}$. A similar half liter of nitrogen is now run into the flask and the pressure rises to B. Altho the total pressure is that of the prevailing barometer the partial pressure exerted by the oxygen and by the nitrogen in each case remains $\frac{B}{2}$. The partial pressure exerted by any gas therefore is that fraction of the total pressure which is equal to its proportion (the proportion of the number of its molecules, not its weight) in the whole mixture.

Partial pressure is frequently given in terms of per cent. An analysis of air shows it to contain approximately 21 per cent of oxygen and 79 per cent of nitrogen and other inert gases. At sea level the partial pressure exerted by these two gases (dry) would be respectively:

21 per cent of 760 mm. = 160 mm. partial pressure oxygen.
79 per cent of 760 mm. = 600 mm. partial pressure nitrogen, etc.

At higher altitudes the same percentages hold but the barometric pressure is reduced and the partial pressure of each gas is proportionately decreased. For example, with a barometer of 750 the partial pressure of oxygen is 151 mm. and nitrogen 569.

From these considerations it might appear that, as gas composition expressed in per cent is independent of barometric variation, it is superfluous to consider partial pressures which fluctuate with the barometer. In physiological work, however, it is partial pressure which is of critical importance. As will be seen in a subsequent section, the solution of gases in liquids is determined by the partial pressure, and not by the percentage of each gas in a mixture. The body gets its oxygen supply by diffusion thru the moist membranes of the lungs, and is therefore dependent upon the partial pressure of oxygen, and largely independent of the amount of nitrogen with which it is mixed. This point is illustrated by the difference in behavior of a man and a burning candle, under alteration in air composition. A candle is a well known and usually a practical test for sufficient oxygen in the air so that a man can safely breathe in such places as a well or a silo. But man and candle are profoundly different. The burning candle is dependent upon the percentage composition of the air, and is largely independent of the partial pressure of oxygen. A candle can be made to burn at almost any altitude, and only becomes extinguished when the size of the flame increases to such an extent that most of it is too far from the wick to maintain an ignition temperature. A man, on the other hand, is in

danger when he reaches an altitude where the partial pressure of oxygen is insufficient for his blood to take up enough oxygen for his needs. The reverse of this behavior of man and candle is seen in an atmosphere partially depleted of oxygen, but at a normal pressure. The candle becomes extinguished when the oxygen falls to 15 or 16 per cent, or about 114 mm. partial pressure, equivalent to the oxygen pressure at an altitude of 5500 feet above sea level, approximately that of Denver, Colorado, where people live healthy lives and candles also burn normally. A man is only slightly affected by an hour or two in 15 per cent of oxygen at sea level and collapses only when the oxygen percentage decreases to a partial pressure of 76 mm., which is about half that at sea level. This comparison may be carried even further. An atmosphere containing 5 per cent oxygen and compressed to 4 atmospheres pressure (the partial pressure of oxygen will then be nearly normal, or 152 mm.) will maintain a man perfectly in respect to oxygen, but a candle cannot be lighted. Likewise in an atmosphere of pure oxygen of a pressure of only 152 mm. a man is entirely normal, while a candle burns with much more than ordinary rapidity.

Influence of Temperature upon Volume.

Gases, if restrained only by barometric pressure, increase in volume as the temperature rises. The rate of expansion is the same for all gases, and for each degree rise of temperature the increase is $\frac{1}{273}$ of the volume at 0°C. The general formula for the relative volumes is $\frac{V}{V'} = \frac{273 + t}{273 + t'}$, in which V and t are the initial volume and temperature and V′ and t′ the final conditions. Thus in passing from 20°C. (ordinary room temperature) to 38° (lung temperature) a gas increases in volume in proportion to $\frac{273 + 38}{273 + 20}$ or 106:100, and in passing from 38° to 20° the decrease in volume is expressed by $\frac{273 + 20}{273 + 38}$ or 94:100. As the gas expands with rise of temperature, but without change of pressure, as in a heated room, the weight of the amount in unit volume falls correspondingly.

Rôle of Water Vapor.

In the lungs the pressure of water vapor is an important factor, and must always be taken into account. It is the more necessary to keep this in mind because in gas analysis percentage readings are ordinarily made upon the basis of dry gas, altho actually the gases are completely saturated with water vapor; and strange as it seems, no cor-

rection for water vapor is necessary in the analytical calculation. The reason no correction is needed is that in a wet gas burette all the measurements are made with the gases saturated with water vapor. The absorbing reagent (e.g. alkali) takes out one of the constituent gases (e.g. carbon dioxide) and part of the water vapor; but when the remaining gas is drawn back into the burette it is again saturated with water vapor. The volume of vapor in this second reading is less than in the previous reading in exactly the same proportion that the absorbed gas bore to the other gases estimated dry. Thus a correct percentage of the absorbed gas to the total gases of the sample, apart from water vapor, is obtained.

In converting the percentage of the absorbed gas into terms of millimeters partial pressure, however, the water vapor present in the original gas mixture under analysis must be taken into consideration. The water vapor in it exerted a partial pressure, and as the sum total of all the partial pressures of all the gases plus the pressure of water vapor only equals the barometric, the pressure of water vapor thus reduces the partial pressure of every other constituent. When the gas mixture is fully saturated with water vapor at a certain temperature, as air in the lungs is saturated at body temperature, the correction for vapor pressure is wholly a function of the temperature and is entirely independent of the barometer. It is necessary merely to subtract the water vapor pressure from that of the prevailing barometer and to consider the resultant value as the total dry gas pressure. The partial pressure of water vapor at 20°C. is 17.4 mm.; thus wet air at 760 mm. and 20°C. will have the oxygen partial pressure given by:

$$0.21 \times (760 - 17.4) = 155.9 \text{ mm. of oxygen.}$$

The same air when dry contains:

$$0.21 \times 760 = 159.6 \text{ mm. of oxygen.}$$

Fortunately in physiological work it is seldom necessary to consider partial saturations with water vapor, since gases inhaled into the lungs become fully saturated with water vapor at the temperature of the body and correction can be made upon that basis. In men ascending to great altitudes the water vapor in the lungs plays a particularly important part, for as this factor remains constant at 50 mm., it becomes an increasingly large percentage of the total pulmonary contents. The constancy of the water vapor thus reduces the pressure of oxygen in the lungs more rapidly than it is reduced in the atmosphere, as the ascent rises to greater and greater heights. At a barometer of 50 mm., if such a height were attainable, the lungs would contain no air, but only water vapor.

Standard Conditions.

For comparison of gas volumes it is essential that they be referred to standard conditions of temperature, pressure, and moisture, that is, as they would be at 0°C. 760 mm. pressure, and dry. If the temperature and prevailing barometer are observed, the volume of gas under any condition can readily be converted to standard conditions. For this conversion the general formula used is:

$$\text{Vol. of (dry) gas at } 0°\text{C., } 760 \text{ mm.} = \text{Vol. observed} \times \frac{(B - W) \times 273}{760 \times (273 + t)}$$

B = prevailing barometer
W = partial pressure of water vapor
t = observed temperature

Solution of Gases in Fluids.

In order to operate fully and rapidly the principle next to be discussed, that defining the solution of gases in liquids, requires very large surfaces. The form in which this principle is usually stated applies only to equilibrium; but equilibrium is actually approached very slowly, and is difficult to produce experimentally. It is best approximated by shaking the gas and fluid together so as to expose the large surfaces and small masses of bubbles, drops and foam, or by rolling the vessel so that a film of liquid is exposed on the wall of the vessel and continually renewed.

In the lungs, however, the blood is spread into extremely fine streams in the capillaries, which are also so numerous that the total surface is enormous; and yet, as the total cross-section of the stream is very large, the rate of flow is correspondingly slow. A virtually complete equilibrium of gas pressures between the alveolar air and arterial blood is thus attained, and this is accomplished almost instantaneously. Practical use of this quick and complete equilibration of gases is made for the purpose of determining the concentration of any foreign volatile substance in the blood. A small volume of air in a rubber bag or spirometer is rebreathed four or five times, and an equilibrium between this air and the gas pressures of the venous blood (subject to certain limitations) is thus attained. The figures obtained from such determinations of the pressure of any foreign gas in the blood are multiplied by either the coefficient of solubility or the more convenient coefficient of distribution of the gas; and the results show the concentration of the substance in the blood. These results, when multiplied by the body weight, indicate approximately the total amount in the body.

Law of Henry and Dalton.

This law defines the influence of pressure upon the solution of gases in fluids at equilibrium. It states that the amount of each gas that is dissolved in a fluid at any given temperature is directly proportional to the partial pressure of that gas acting upon the fluid, and is totally independent of all other pressures. By means of this principle we can find, for example, the answer to the question, raised in the next section what amount of carbon dioxide will dissolve in water at 60°C. when the total pressure of carbon dioxide is 611 mm. The law tells us that the water will reach $\frac{611}{760}$ of the amount defined by the coefficient of solubility, which is 359 cc. of CO_2 per liter of water, when the gas is separated, dried, cooled to 0° and measured under 760 mm. pressure.

Conversely, if a certain sample of water contains 100 cc. of dissolved carbon dioxide per liter at 60°, we can calculate the partial pressure. The water contains $\frac{100}{359}$ of the amount that it would dissolve at this temperature and 760 mm. partial pressure of this gas; and by applying Henry's law $\frac{100}{359} \times 760 = 212$ mm. It does not matter at all what other gases are also in solution in the fluid, nor their amounts or pressures. Nor does any hydrostatic pressure to which the liquid may be subjected have any influence upon the partial pressure of the dissolved gas.

There are three forms of expression for the solubility of gases: (1) coefficient of solubility, (2) solubility by weight, and (3) coefficient of distribution.

Coefficient of Solubility.

A gas in contact with a fluid dissolves until the partial pressure of the gas in solution equals the partial pressure of the remaining undissolved gas. The amount of gas which it is necessary to dissolve in any fluid to balance a given partial pressure of the gas varies with the nature of the fluid and the temperature. Altho it is a general rule that with rise in temperature less gas must be dissolved to produce any given pressure, the influence upon the amount dissolved which is exerted by temperature is subject to no simple rule but is specific for each gas and each liquid. It is therefore necessary to determine experimentally the solubility of each gas in each fluid at various temperatures. This value is known as the coefficient of solubility for the particular condition.

It is customary to express the coefficient of solubility for any given temperature as the amount of the gas in a unit volume of fluid which is in complete equilibrium with the gas at a partial pressure of 760 mm. and the given temperature. But this amount of dissolved gas is not stated at the volume that it would have as a free gas at the given temperature, but at 0°C. and 760 mm. Thus to say that the coefficient of solubility of a certain gas in water at 38°C. is 0.05 means that water at that temperature dissolves 5 volumes per cent of the gas and that if all of the gas is then pumped out of 100 cc. of the water, dried, cooled to 0°C. and measured at 760 mm., it would be 5 cc.

Not only the total gas pressure acting upon a fluid at 760 mm., but also the vapor pressure of the fluid itself at the given temperature must be taken into account. Passing a gas thru a flask of water, until no more is taken up, does not give the solubility at the pressure at which the gas stream is supplied. Thus, for example, the coefficient of solubility of carbon dioxide in water at 60°C. is given as 0.359. This does not mean that if the total gas and vapor pressure upon the water is 760 mm., the amount of gas dissolved in one liter will be 350 cc. The partial pressure of carbon dioxide acting upon the water under the conditions here defined is in fact not 760 mm., but 760 minus the water vapor pressure at 60°, which is 149 mm. The partial pressure of the carbon dioxide is therefore 611 mm. In order to produce a pressure of 760 mm. of carbon dioxide in water at 60° it would be necessary to force CO_2 into the flask under a total pressure of 760 plus 149 mm., or 809 mm. absolute, or 149 mm. gage pressure.

Solubility by Weight.

The solubility of gases in fluids is sometimes expressed in terms of the weight of gas in solution in unit volume of the fluid at a given temperature and normal atmospheric pressure. It is customary to give the weight of the gas found in unit volume when the fluid is exposed to 760 mm. of total pressure, that is, gas and water vapor, and not as in the case of the solubility coefficient with the partial pressure of the gas itself at 760 mm. The shift in base is somewhat confusing, but suitable correction is readily made. Thus a table contained in books of reference gives the solubility of carbon dioxide at 60°C. with a coefficient of volume solution of 0.359 or 359 cc. per liter, while the weight of the gas dissolved at this same temperature is given as 0.0577 gram per 100 cc. of water, or 0.577 gram per liter. These two amounts do not agree, for one cubic centimeter of carbon dioxide weighs 0.002 gram, and 0.577 gram of carbon dioxide corresponds to 288 cc. of the gas. The latter figure corresponds however to a partial pressure

of 611 mm. which (see above) is equivalent to 760 mm. minus the pressure of water vapor at 60°C.

Coefficient of Distribution.

Still a third mode of expression has been found by the authors more convenient than either of the two preceding conventional forms for the solubility of gases in fluids. It is the coefficient of distribution. By this term is meant the relative weights of gas in equal volumes of the gas mixture and of the fluid which are in gaseous equilibrium. In expressing the ratio of distribution it is customary to take the concentration of the gas phase as the unit. Thus in a system in which each liter of air contains 3 mg. of the substance, and the fluid in equilibrium with it contains 12 mg. per liter, the ratio is 3 : 12, and the coefficient of distribution would be given as 1 : 4, or merely as 4.

The use of the coefficient of distribution is particularly convenient in dealing with the absorption of gases thru the lungs into the blood. As stated here the term coefficient of distribution is very similar to the "proportionality constant" (K) used in the thermodynamic presentation of Henry's law, in which the partial pressure (p) of any volatile substance present in small amounts in a solution is proportional to its molar concentration, (C). That is

$$p = KC, \text{ or } \frac{C}{p} = K$$

The value of K is of course dependent upon the nature of the substance dissolved and of the solvent fluid, and upon the temperature. The distinction between the proportionality constant and the coefficient of distribution (D) lies in the fact that the latter is given in the same terms of molar concentration for both the solution and the vapor. Thus

$$\frac{C}{C'} = D$$

Here C is the concentration in the fluid, and C′ the concentration in the vapor phase; and both are expressed in mols, or both in grams per liter.

Behavior of Vapors.

A vapor differs from a gas by the fact that, while the latter under ordinary conditions exists only in the gaseous state, the former is the gaseous phase of a substance which (as in the case of water vapor above discussed) can exist also in the form of liquid at common temperatures and pressures. Thus, for example, at room temperature a flask partially filled with ethyl ether may contain both liquid ether and ether vapor; while on the contrary hydrogen, nitrogen, carbon

dioxide, etc., are encountered under these conditions only as gases. At very low temperatures and high pressures these typical gases are partially condensed to liquid form and may then be present as vapors.

The distinction between gases and vapors is necessary because of the difference in behavior of these two classes of substances in respect to alterations of temperature and pressure. The behavior of a vapor mixed with air is in fairly close accord with the gas laws and can be so treated, providing that none of the substance is present in liquid form, and that there is no passage from the gaseous phase to the liquid. The more dilute the mixture of a vapor in air the more nearly does it conform to the gas laws. But alterations of phase introduce special considerations for vapors.

When a volatile fluid is exposed to the air, a portion evaporates and exists mixed with the gases of the air as the gaseous or vapor phase of the substance. If the air and fluid are enclosed in a vessel, a point will finally be reached at which equilibrium is established between the fluid and vapor and no further volatilization occurs. A pressure gage connected with the vessel shows that in consequence of the addition of the vapor to the air the pressure has risen. If the flask was closed while containing air and liquid, but before the liquid had evaporated appreciably, the increase in pressure resulting from the volatilization of the fluid at the existing temperature is known as the vapor pressure. The vapor pressure of a liquid in equilibrium with the pure substance increases with rise in temperature much more rapidly than does the pressure of a true gas; when separated from its liquid, however, it follows the law of Charles. Different liquids have different vapor pressures for the same temperature; but at the boiling point of any fluid the vapor pressure equals the barometric pressure prevailing upon the fluid. The lower the barometer the lower the boiling point. Thus water at 40°C. has a vapor pressure of 55 mm., and when the atmospheric pressure is reduced to 55 mm., it therefore boils.

Thus the treatment of vapors in terms of the gas laws reaches a limit at the vapor pressure. To state the matter broadly and in practical terms: a vapor ceases to behave as a gas, and tends to condense into the liquid form whenever the weight per volume of air, or the partial pressure of vapor measured at the existing temperature and barometric pressure, equals the maximum weight or partial pressure of the vapor which can be developed by volatilization in a closed vessel at the given temperature. To illustrate, let us assume that we are dealing with a liter of air at 760 mm. and 30°C. containing 2 grams of ether vapor. The ether in this mixture will behave essentially as a true gas during any decrease of pressure, due to enlarging the space, or any increase of temperature. If on the contrary the space were contracted at the same

time that the temperature was decreased to 20°C., so that the pressure remained 760 mm., the air at that temperature would contain an amount of ether corresponding to 2.08 grams per liter. Condensation must then take place; for at 20°C. the vapor pressure, or maximum possible partial pressure of ether, is 442 mm., which is equivalent to 1.9 grams per liter. Therefore 0.18 gram per liter will condense and pass into the liquid state. On the other hand, if the same mixture were made up at 30°C. and were maintained at this temperature, but compressed to half its volume (a pressure of 1,520 mm. of mercury), the partial pressure of ether would be doubled, so that 4 grams would be contained in one liter. But this condition cannot persist, since the limit of partial pressure of ether at 30° is 648 mm., which is equivalent to 2.58 grams per liter. On this account 1.42 grams will be condensed out as liquid ether. Subject to these limitations, however, the weight of a liter of vapor is calculated by dividing the gram molecules of the substance by the gas constant and treating it in the manner described for gases.

Solubility of Vapors.

The solubility which particularly concerns us here is that of vapors in blood at body temperature: in other words, the coefficient of distribution under the conditions existing in the lungs and determining the absorption of vapor when it is inhaled. The solubility in blood has been determined directly for very few substances.* In general it is slightly (about 10 per cent) less than in water; it is decreased in about the proportion that the water in blood is diluted by its solid constituents. This statement regarding the solubility of ethereal substances in blood is based on the experience of the authors; it contradicts a belief common among physiologists and biochemists that the lipoids in blood add considerably to its solvent power for ethereal substances. The purpose of the discussion here is to point out how such data as exist for the solubility of volatile substances in water may be so applied as to afford approximate values for blood. When they react with hemoglobin or some other constituent of the blood, another factor enters.

Substances which can exist both in liquid and vapor form at ordinary temperatures vary in the extent to which the vapor pressures of solutions of the substances in water are decreased below those of the pure liquids. There are wide differences in behavior between those sub-

* There is great need for a systematic determination of the solubilities of all the more common volatile organic substances in blood at body temperature, together with their possible combinations with hemoglobin. The chemical industry should supply the funds for this investigation, which would yield results of fundamental importance for the health of its employees. We suggest that the U. S. Bureau of Standards should be asked to take charge of developing a table of such data.

stances whose liquids are miscible with water in all proportions and those whose liquids are very slightly soluble in water; and there are all gradations between these extremes. No single simple formula applies to all. In order to be of practical use here, and not erroneously applied, Raoult's law, which is more general than the law of Henry, and other theoretical matters, would require not only full discussion, but careful limitation. A textbook of physical chemistry may be consulted; but even in the case of substances suitable for direct application of Raoult's law, accurate data are often lacking. Even the solubilities in water of ethereal substances in liquid form are in many cases undetermined; and such data as are available are for the most part rather rough approximations. Very few solubilities have been determined directly for vapors in water.

The solubility of a vapor in water at a certain temperature can, however, usually be estimated by combining the data from two tables in books of reference: the table showing the vapor pressure of the pure liquid, and the table showing the solubility of the liquid in water. For solutions in water of substances which do not themselves dissolve water to any great extent, a close approximation of the coefficient of distribution between the vapor phase and the dissolved phase is obtained by assuming that the amount of the substance that would be dissolved under a pressure equal to the vapor pressure of the pure liquid is the same as the amount dissolved when the substance in liquid form has been freely exposed to water. Below this pressure the concentration and pressure vary proportionally in accord with the law of Henry.

The general principle of Raoult's law applying to this matter is that the vapor pressure of an ethereal substance in solution is the same as that of the substance in liquid form in which a certain amount of water is dissolved, and in which the molar concentration of the ethereal substance is thus reduced. As the molar concentration is decreased the vapor pressure is decreased proportionally. Thus if two dishes, one A containing water, and the other B containing the pure liquid substance, are put together under a bell jar and left until equilibrium has been reached by the passage both of water vapor and ethereal vapor between the contents of the dishes, the concentration of the ethereal substance in solution in the water in A will be that which is in equilibrium with a vapor pressure less than that of the pure ethereal liquid, which was originally in B, in proportion as the pure liquid in B has itself become diluted by dissolving water.

The next chapter will show how large and important is the part which solubility plays in the absorption, distribution and elimination of volatile substances thru the lungs and in the body.

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Chapter V.

Principles Determining Absorption, Distribution and Elimination of Volatile Substances.

Noxious gases and vapors, other than irritants and simple asphyxiants, exert their action only after absorption into the blood. The intensity of the action, and in some cases even its character, are determined by the concentration in the blood, that is the amount in unit volume of blood, and the duration of its stay, and not merely by the inherent toxicity of the substance. Indeed the effect upon the body is proportional to the product of these three factors: concentration, duration, and toxicity. In the consideration of the physiological action of volatile substances the mechanisms of absorption, elimination, distribution and destruction within the body are therefore of an importance equal to that of their specific toxicity. For example, ethyl alcohol is inherently more toxic than an equal amount of methyl alcohol, but the difference in the rate at which the concentrations in the blood decrease renders methyl alcohol a much more dangerous poison than ethyl alcohol.

Reactive and Nonreactive Gases.

The gases and vapors which exert their action after absorption into the blood are of two classes: reactive and nonreactive.

Reactive substances are altered within the body and are eliminated to a large extent in forms other than those in which they were absorbed. The toxicological action may be exerted either by the substance in its original form or by the products of its reaction. Ethyl alcohol is an example of a reactive vapor which exerts its action before its destruction has taken place; aniline is an example of a vapor which exerts its main action thru the products arising from its reaction in the body.

Nonreactive substances are not altered to any appreciable extent in the body and are eliminated in the same form in which they are absorbed. The aliphatic hydrocarbons are examples of nonreactive gases and vapors.

Principles of Absorption of Nonreactive Gases.

It is important to realize that there are definite and very practical principles which control the absorption, distribution and elimination of nonreactive gases and vapors.

The rate at which a gas or vapor is absorbed into the body and the amount the body can hold vary greatly according as the gas is more or less soluble. In general the solubility of a gas in blood is only slightly less than its solubility in water. The capacity of the various tissues to dissolve gases varies; it is low in bone and often high in fat; but with most gases the average for the body as a whole is probably nearly the same as the solubility in blood. This is true at least for those gases and vapors which have been chiefly studied in this relation; for example, ethyl ether, hydrogen and nitrogen. The total amount of any nonreactive gas or vapor that the body will take up is dependent both on solubility and upon the concentration in the air breather.

The rate of absorption is directly proportional to the concentration of the gas or vapor in the air breathed. For calculation of the rate of absorption, the concentration is best expressed in milligrams of the volatile substance per liter of air. The concentration that is effective is, however, not exactly the concentration in the air of the room; it is the concentration which results when the air is warmed to body temperature and saturated with moisture. It is the somewhat reduced concentration under these conditions, as they obtain in the lungs, which induces diffusion into the blood passing thru the lungs. At the saturation point the total amount of gas in the body is directly proportional to the concentration in the atmosphere with which the blood and body as a whole have come into equilibrium. From twice as high a concentration the body will absorb twice as much of the gas or vapor.

The third factor influencing the rate of absorption is the pulmonary ventilation. The rate of absorption depends upon the volume of air breathed and the amount of gas thus brought in contact with the blood in the lungs, but not that which merely enters the dead space. Respiration is particularly important in determining both the rate of absorption and of elimination in the case of quite soluble gases and vapors; but it is comparatively unimportant in respect to relatively insoluble gases.

The circulation is the fourth factor and is largely determinative of the rate of absorption and elimination of gases of relatively low solubility, while for such gases respiration plays a comparatively small part. Thus a condition which would double the volume of air breathed per minute would only slightly affect the entrance or exit of such a gas, so long as the circulation remains constant. But if the circulation were doubled so that twice as much blood would flow thru the lungs each minute, even with respiration unchanged, the rate of absorption and elimination of such a gas would be nearly doubled.

General Process of Absorption.

Figure 4 represents diagrammatically the relations of the circulation, respiration and body tissues. Together these factors constitute the mechanism thru which gases are absorbed. In this diagram the upper chamber represents the lungs. For convenience the ventilation is considered as a continuous flow of air; the inspired air enters at the right and the expired passes out at the left. The partition across the chamber divides the air stream so that a portion does not come in contact with the blood. The area above the partition represents the virtual dead space; thru this space the air passes from inspiration into

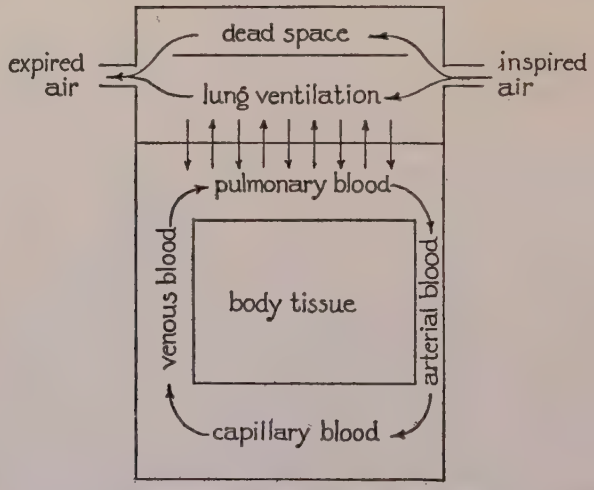

FIG. 4.—Diagram of the respiratory tract to show the relations of the dead space, lung ventilation, blood circulation and body tissue.

expiration without appreciable diffusion of any gas it may contain into the blood. The remainder of the air is the effective pulmonary ventilation, and comes into free diffusion with the pulmonary blood. Virtually complete equilibrium in respect to all gases is almost instantly established between the air and the blood in the lungs, and is continually and accurately maintained.

At the commencement of inhalation any gas which is taken up by the blood in simple solution is carried in the arterial stream to the capillaries, where it diffuses into the tissues. If those tissues and organs thru which the blood flow is large a nearly complete equilibrium between blood and tissues is almost instantly attained. The venous blood therefore leaves the tissues with a concentration of the gas or vapor practically identical with that of the tissues thru which it has passed;

and it then returns to the lungs for a fresh charge. As this process continues, the amount of the gas or vapor, and hence the tension (i.e. the partial pressure of that gas) constantly rise in the tissues. The amount in the venous blood also rises correspondingly and tends to approach that of the arterial. More and more of the gas or vapor is thus carried back to the lungs by the venous blood; consequently a decreasing amount is taken up by the blood from the air in the lungs, and by the tissues from the blood. The limit approached is a state of saturation at which the body will contain an amount of the gas or vapor equal to the product of three factors: namely, the weight of the body

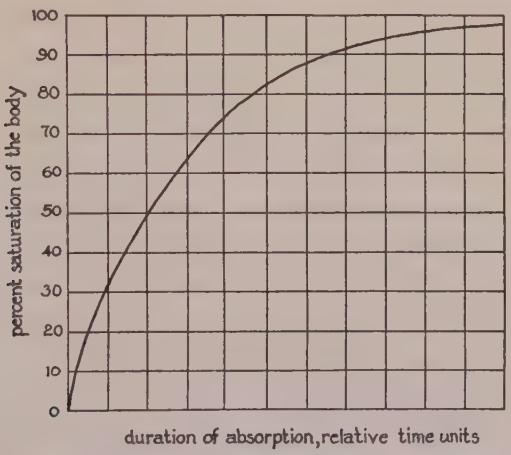

FIG. 5.—Curve of absorption of a nonreacting gas. The value for 100 per cent saturation is that of full equilibrium between the body and the surrounding atmosphere.

multiplied by the concentration of the gas or vapor in the air in the lungs and by its coefficient of solubility at body temperature.

The course of absorption may be expressed as follows: If during any time, t, the body becomes saturated to x per cent of full saturation for the tension inhaled, it will in the next equal period increase in saturation by x per cent of the remaining unsaturation. Thus after twice, and three times this amount of time we shall have

$$x + x\,(1 - x) = 2x - x^2 = \text{saturation after } 2t, \text{ and}$$
$$2x - x^2 + x\,(1 - 2x - x^2) = 3x - 3x^2 + x^3 = \text{saturation after } 3t,$$
and so on.

This type of mathematical expression gives rise to a curve approaching the logarithmic in shape, as illustrated in Fig. 5.

The ordinate of the curve of figure 5 expresses the percentage

saturation of the body with the gas or vapor. The abscissa represents time, but has different values for different gases; its scale, if all the physiological conditions (such as respiration, circulation and body weight) are fixed, depends on the coefficient of solubility of the gas. In other words the absorption of any and all nonreactive gases, and of all concentrations of them follows this curve. The ordinates are always percentages of complete saturation of the particular body weight, by a gas of a particular solubility, and for a particular concentration in the air. For twice the concentration the ordinates, when translated into terms of milligrams per liter or per kilo, would indicate twice the amounts, but in terms of per cent saturation the ordinates are the same for all concentrations. The abscissa is in terms of time; the higher the solubility of the gas and the more active the respiration and circulation, the shorter the distance along the abscissa corresponding to a period of, for instance, 10 minutes. An animal which reaches 20 per cent saturation with a certain gas in 10 minutes will be 36 per cent saturated in 20 minutes, and 75 per cent in 1 hour. If the gas were more soluble, that is if the capacity of the body to dissolve the substance were larger, these percentages might be attained in 20, 40 and 120 minutes; if it were less soluble, after only 5, 20 and 30 minutes.

Mathematical Expression of the Process of Absorption.

In order to express mathematically the part played in absorption by variations in blood flow, respiration, inhaled concentration of the gas or vapor, and its solubility, these factors may be assigned the following symbols:

L—effective pulmonary ventilation, in liters per minute; i.e., respiration minus the volume of air which merely enters the dead space. (See Chapter II.) This is usually about two-thirds of the volume of respiration.

C—concentration of the gas or vapor, in milligrams per liter of inspired air, when warmed to body temperature and saturated with moisture as it is in the lungs. (See Chapter IV.)

K—solubility of the gas; or, more precisely defined, its coefficient of distribution between equal volumes of lung air and pulmonary blood. For ordinary conditions complete and instantaneous equilibrium between arterial blood and lung air may be safely assumed. Thus if for a certain vapor such, for example, as that of ether, K is 15, this figure means that there is always in the arterial blood leaving the lungs, fifteen times as much of that gas in one liter of blood as in one liter of alveolar air; and that this holds true alike during absorption, equilibrium and elimination of the gas or vapor.

G—liters or kilos of blood in active circulation in the body. In other words the effective volume of blood at the time. The volume of blood in man ranges between 5 and 7 per cent of the weight of the body.

B—circulation, defined as the number of liters or kilos of blood flowing thru the lungs in one minute.

A_c—concentration of the gas in the arterial blood, in milligrams per liter.

V_c—concentration of the gas in the mixed venous blood in the right heart, in milligrams per liter.

W—body weight, in kilos.

Using these symbols and definitions, the following simple and useful expressions follow as logically necessary.

LC = the amount of gas inhaled into the lungs per minute. (1)

$LC \times \frac{L}{BK + L}$ = amount of gas again exhaled from the lungs per minute. (2)

$LC \times \frac{BK}{BK + L}$ = amount of gas absorbed per minute into the blood, before any of the blood completes the round of the circulation and returns to the lungs from the venous side; that is, the initial rate of absorption. (3)

$\frac{LCK}{BK + L}$ = amount of gas in milligrams absorbed per liter of blood flowing through the lungs. (4)

$\frac{LCKG}{BK + L}$ = amount of gas absorbed during the first complete circulation of the blood, which is accomplished in the time $\frac{G}{B}$, a period less than one minute even during bodily rest. (5)

$\frac{LCKG}{BK + L} \times \frac{G}{W} = V_c \times G$ = amount of the gas brought back to the lungs by the venous blood during the second round of the circulation. (6)

The amount of the gas which the blood brings back to the lungs from the venous side is added to that which the breathing takes into the lungs; and the sum of the two quantities is distributed between the arterial blood and the expired air in accord with their relative volumes and with the coefficient of solubility. The distribution is always in the ratio BK : L.

These expressions signify that during absorption the arterial blood contains at first far more of the gas or vapor than the venous blood. But as the inhalation of a constant concentration of a gas in the air continues, the concentrations in the arterial and venous blood gradually approach the same value, namely, that of saturation for the concentration of the gas in the air. At all times the mixed venous blood flowing back from the body contains an amount of the gas per liter which is the same as the average concentration in the body as a whole at the moment (in milligrams of the gas per kilo body weight). During absorption, therefore, especially in the earlier stages, the concentration in the venous blood is far below that in the arterial blood. During elimination, on the contrary, the venous blood has a concentration which is the average of the concentration in the body as a whole, while that of the arterial blood is lower than the venous by the fraction thrown off in the breath. Thus

$$V_c\left(1-\frac{L}{BK+L}\right)=A_c, \text{ the arterial concentration during elimination.} \quad (7)$$

The amount of any gas that the body will hold is defined by the expression:

$$CKW = \text{amount of gas in the body at equilibrium with C in the air.} \quad (8)$$

As pointed out above, the maximum amount of a gas that can be absorbed is not a fixed absolute quantity, but is proportional to the concentration of that particular gas in the air, and proportional also to its solubility. When respiration and circulation remain uniform and normal, the rate of absorption is such that, if a certain percentage of saturation is taken up in one minute, the same percentage of the remaining unsaturation will be absorbed in the second minute, and so on thereafter. Thus if saturation be taken as 100, and if one per cent of this amount is absorbed in one minute, one per cent of 99 will be absorbed in the second minute; and one per cent of 98.01 in the third minute, and so on. The absorption is thus comparatively rapid at first, then slower and finally infinitely slow. It is not practical therefore to determine the time when equilibrium of intake and elimination will be reached; but is is often convenient for purposes of calculation to use the time required to reach 50 per cent saturation, $\frac{CKW}{2}$, or some other percentage of saturation.

The time required to reach a certain percentage saturation x, may be derived as follows. Let A be the amount absorbed in the time t;

then, since CKW is the maximum, or limiting amount, that can be absorbed and since

$$\frac{dA}{dt} \propto (CKW - A), \text{ therefore } \frac{dA}{dt} = k(CKW - A).$$

Integrating with θ as the constant of integration.

$$\ln [\theta (CKW - A)] = -kt, \text{ and } \theta (CKW - A) = e^{-kt}.$$

$$A = CKW - \frac{e^{-kt}}{\theta}, \text{ but when } t = O, A = O, \text{ and therefore } \theta = \frac{1}{CKW}$$

Accordingly,

$$A = CKW (1 - e^{-kt}). \qquad (9)$$

Now if x equals the percentage of saturation reached in time, tx,

$$x.CKW = CKW.(1 - e^{-kt_x}).$$

$$\frac{1}{1-x} = e^{-kt_x}, \text{ or } kt_x = \ln \frac{1}{1-x}$$

$$t_x = \frac{2.3}{k} \log \frac{1}{1-x} \qquad (10)$$

Since at the start $A = O$, therefore, $\frac{dA}{dt} = k(CKW)$; and from general consideration initially $\frac{dA}{dt} = \frac{LCKB}{BK + L}$; combining these two expressions we have $k = \frac{LB}{(BK + L)W}$, which can be substituted in (9) and (10).

The use of the half saturation time, or the time of any definite percentage of saturation, is particularly convenient because it is the same for all concentrations of any one gas, so long as respiration and circulation are uniform. But the greater the solubility of a gas, the longer is the time required to reach half saturation, and the greater the absolute amount constituting half saturation.

For an average human adult at rest with a normal volume of respiration and circulation, the time of half saturation for a gas or vapor of $K = 15$, such as ethyl ether, is about 2.5 hours, while for one of $K = 0.014$, nitrogen, it is about 7 minutes, and for 90 per cent of saturation about 22 minutes. For a child, owing to the more active metabolism and greater relative volume of breathing and circulation in relation to body weight, the time required to reach half saturation, or any other definite percentage, is correspondingly less. The same relation holds

true in an adult, when respiration and circulation are increased by exercise, or by the pharmacological action of the gas itself, or in any other way.

The absorption of any absolute amount of gas, for example the anesthetic amount of ether, is effected very slowly when a low concentration of the gas is inhaled; but with a far more than proportional rapidity when the concentration in the air is high. The rates of absorption are not expressed by straight lines, but by exponential curves which rise rapidly at first and then more and more slowly. In the absorption curves of all concentrations of a given gas, points having equal abscissae have ordinates which are proportional to the concentration. An absolute amount in milliliters may therefore be only a relatively low percentage of the saturation limit (CKW) of a high concentration, but a high percentage of the limit, or even exceed the limit, for a low concentration.

The influence of respiration, circulation, and the solubility of the gas upon the time required to reach 50, or any other per cent of saturation, is expressed by the formula:

$$\frac{t_x}{t'_x} = \frac{\frac{BK + L}{LB}}{\frac{B'K' + L'}{L'B'}} \qquad (11)$$

Using this formula and substituting various values of K, so as to see the effect that solubility has, not only on the rate of absorption, but also on the parts played by respiration and the circulation in effecting absorption, we reach results of great utility. Thus with a gas of a solubility as low as 0.01, even a doubling of the respiration scarcely affects the rate of absorption or of elimination, while a doubling of the circulation of the blood induces a nearly proportional increase of the rate of absorption and elimination. On the other hand, with a gas of solubility 10, alterations of the circulation of the blood have an entirely negligible effect, while the rates of absorption and elimination rise and fall almost in proportion to the volume of respiration. The relative amounts of time in hours or fractions of an hour required to effect, for instance, 50 per cent saturation are shown in the following table:

	$B = B' = 1$		$L = L' = 1$	
	$L = 1$	$L' = 2$	$B = 1$	$B' = 2$
$K = 0.01$.....	1.01	1.005	1.01	0.51
$K' = 10.0$.....	11.0	6.0	11.0	10.5

Elimination of Nonreactive Gases.

Nonreactive gases and vapors are eliminated largely thru the lungs; the urine and other secretions carry away relatively small amounts. The concentration of the gas dissolved in the urine corresponds to that in the blood passing thru the kidneys at the moment the urine is secreted. The elimination thru the lungs follows definite principles which are similar to those of absorption.

At the termination of absorption the body contains an amount of the gas which is equivalent to full equilibrium with some tension of the gas, altho this may be much lower than the inhaled concentration with which the body has been brought to partial saturation. If none of the gas is eliminated, the body forms a closed and static system in which the gas is distributed to the various tissues and to the air in the lungs in proportion to their capacity to dissolve the gas. The concentrations in the arterial and venous blood, under these circumstances, are the same. When elimination begins and part of the air in the lungs is replaced by fresh air, a part of the gas is carried away in the expired air and the concentration of the gas in the arterial blood leaving the lungs is reduced below that in the venous blood coming to the lungs.

The following expressions give the relations of the factors concerned in elimination:

$$V_eB \times \frac{L}{BK + L} = \text{amount of the gas or vapor in milligrams eliminated in one minute.} \quad (12)$$

$$V_eG \times \frac{L}{BK + L} = \text{amount of the gas or vapor in milligrams eliminated in one round of the circulation.} \quad (13)$$

Since the body is 100 per cent saturated for some tension of the gas at the beginning of elimination (namely that developed in the pulmonary air under the static equilibrium above mentioned), the loss of the amount of gas expressed by equations 12 or 13 decreases this percentage saturation to an extent expressed by the fraction:

$$\frac{\text{Gas or vapor eliminated in first period}}{\text{Total amount of gas or vapor previously absorbed}} = \text{Rate of elimination in per cent of the body content.} \quad (14)$$

During a second period of the same duration a further but slightly less amount of the gas or vapor will be eliminated, and this amount is the same percentage of the gas remaining in the body. Obviously this is the same type of mathematical expression as that for the rate of absorption in equations 1 and 2, and the curve would be the reverse

of that given in Figure 5. The elimination is, therefore, rapid in the beginning and becomes more gradual until the curve is nearly horizontal, indicating that the final rates of elimination are very slow.

Rate of Saturation of Particular Tissues or Organs.

These principles apply to the absorption of volatile substances in the body as a whole, but not necessarily to any one tissue or organ alone. Certain gases and vapors, particularly the anesthetic hydrocarbons, exert their action specifically upon one tissue and are largely inert in regard to others. Such action may or may not correspond to varying degrees of capacity to dissolve in the tissue. It is, therefore, important to consider the factors governing absorption by any one tissue or organ.

The maximum amount of the inhaled gas which any organ or tissue can absorb at a given tension is determined by the solubility of the gas in that tissue. The rate at which the gas accumulates in the particular tissue depends both upon the solubility of the gas in that tissue and also upon the amount of the gas brought to the issue in any period of time. The latter factor is determined by the blood supply in relation to the bulk of the tissue. Thus a tissue with a comparatively low solubility for the gas and a large blood flow approaches saturation rapidly, while a tissue of high solubility and small blood flow approaches saturation much more slowly.

During bodily rest it may be estimated that approximately 80 per cent of the blood passes thru 20 per cent of the tissues in each round of the circulation; the remaining 80 per cent of the tissues receive only 20 per cent of the blood. Muscles, bone and fat, which together constitute the bulk of the tissues of the body, receive a comparatively small blood flow. The flow to the brain, viscera and glands is large. This latter group of organs therefore approaches saturation at a much more rapid rate than do the muscles, bone and fat. The same relation holds true of elimination.

The rate of saturation of tissues with a large blood supply follows closely the concentration of a gas or vapor in the arterial blood. The concentration in these tissues rises therefore at first much more rapidly than in the tissues with a smaller blood supply, but the less rapidly saturating tissues act as a buffer to prevent immediate and complete equilibrium. This is the case both during the absorption and elimination of the gas. During absorption the tension of a gas in any tissue cannot rise above the tension of gas in the arterial blood, nor can it fall below this limit during elimination. The tissues of small circulation and slow saturation and desaturation influence the concentration in the venous blood, and consequently that in the lungs and arterial blood also.

Prior to saturation, and particularly at the beginning of inhalation, the concentration of the gas in the arterial blood may fluctuate considerably under the influence of changes in circulation and respiration. If the action of the gas is, for example, upon the brain, an organ of extremely large blood supply, as is the case with the anaesthetic hydrocarbons, the physiological response follows the concentration in the arterial blood extremely closely, and is little influenced by the total amount absorbed into the body. With such substances the pharmacological activity follows rather closely the concentration of the gas in the air inhaled; or more exactly expressed, it is almost exactly proportional to the concentration in the air in the lungs. On the other hand, the concentration in the mixed venous blood may still be quite low, for it depends upon the average degree of saturation of the entire body. The concentration in the peripheral venous blood indicates merely the degree of saturation attained in the particular organ from which the blood is returning.

Absorption of Volatile Substances thru Channels other than the Respiratory Tract.

Volatile substances may be absorbed thru channels other than the respiratory tract. The ingestion of alcohol, the administration of ether by way of the colon, and the absorption of aniline thru the skin are examples. Under these circumstances the volatile substances enter the venous blood instead of the arterial; and this is different in principle from absorption thru the respiratory tract. The venous blood from the place of entrance carries the dissolved gas or vapor to the right heart, where it is diluted by the entire venous stream, and then passed thru the lungs. The volume of breathing and rate of blood flow then determine the distribution of the substance between the air to be expired and the arterial blood to be distributed to the tissues of the body. The process is unlike that of absorption thru the lungs, but is similar to that of elimination, as discussed above, with this exception: the concentration of the gas or vapor in the mixed venous blood does not express the average of the concentration in all the tissues of the body. Furthermore, altho the substance is being eliminated, the concentration in the tissues rises instead of falling; for the absorption under these circumstances is in the nature of a redistribution. With these modifications the equations given under the discussion of absorption and elimination apply alike to absorption thru channels other than the respiratory tract. The factors are the same, namely, the circulation, respiration and coefficient of distribution of the gas between blood and air in the lungs; but they interact in different associations when absorption occurs thru channels other than the pulmonary tract.

Absorption and Elimination of Reactive Gases.

The character of the process concerned in the absorption of reactive gases is in general the same as that for nonreactive gases, but with this difference: the reaction and consequent destruction of the gas prevent the attainment of equilibrium. The venous blood does not return to the lungs carrying the amount that would be anticipated from equation (6). The course of absorption is influenced by the rate of alteration of the gas or vapor within the body and this rate has been determined only in the case of a few substances, notably ethyl alcohol and ethyl iodide and in these cases only approximately. Neither of these approximations, in the one case an oxidation, in the other probably a hydration, is sufficiently precise for mathematical analysis; nor do the values determined apply to other substances.

The elimination of reactive substances is likewise influenced by their alteration within the body. The amount of the substance eliminated is less than the amount absorbed. The mathematical analysis of elimination presented in the previous section applies to reactive substances only in regard to the exhalation thru the lungs of a certain proportion of the amount brought to them by the venous blood, and not to the total quantity in the body. The curves of absorption and elimination of reactive substances do not correspond to that given in Figure 5.

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Chapter VI.

Classification of Noxious Gases and Vapors.

In the introductory chapter a convenient classification of the noxious gases is given. In the present chapter and its accompanying table the names, chemical formulas and physical characters of the gases which occur most often in modern industry are set down along with the general nature of their physiological action. In this table they are listed in their chemical sequence, so that they may be easily found. But in order that the reader who consults this table may see immediately what is the nature of the action of each gas on men and animals, a column has been placed at the right of the table showing to which of the various toxicological classes each gas must be assigned in accord with its physiological action; and a reference is also given to the chapter where this action is described.

In succeeding chapters the chemical order will be largely neglected, and the particular gases will be dealt with under the different classes of physiological action. In order to save space and the reader's time, general descriptions of the various types of physiological action will be given with lists of the substances producing these effects, instead of the endless detail and repetition which would be involved in following the chemical order and treating each gas separately. A few gases must be treated separately, because their special physiological characteristics differentiate them from all others. With these few exceptions, each gas will be described only in association with its physiological relatives in the family of gases.

There are probably many other noxious gases beside those here listed. An indication of the probable pharmacological action of these little known or rarely occurring gases may usually be obtained by noting the toxicological character of related and analogous substances in the chemical order.

Character of Substances Included.

The list of noxious substances here presented is limited to those which are volatile, either gases or vapors. Dusts are not included. Thus mercury finds a place in the table, for the reason that its vapor pressure at ordinary temperatures is sufficiently high for the substance

in gaseous form to induce poisoning. Lead, on the other hand, is listed here only as the alkyl compound. That compound is truly volatile; but metallic lead at ordinary temperatures does not exist as a gas. Poisoning from the inhalation of the fumes of the metal, or of its inorganic salts, results not from the gas or vapor, but from the substance in the form of dust. Such dust may indeed arise from the condensation of lead vaporized at high temperatures; but the line of what is to be included in this book must be drawn somewhere, and dusts have been ruled out. We feel justified in this for the reason that the hygienic aspects of dusts are in many respects quite different from those of gases. Furthermore they already have their own extensive literature.

Physiological Classification of Gases.

The classification of gases according to their physiological actions divides them into four main groups and several subgroups, which will here be described somewhat more fully than in the first chapter. But details will still be kept to later chapters.

TABLE OF NOXIOUS GASES LISTED ACCORDING TO CHEMICAL COMPOSITION AND CLASSIFIED ACCORDING TO THEIR ACTION.

Name	Formula	Ordinary Condition	Boiling Point, Degrees Centigrade	Nature of Physiological Action; Classification
Inorganic Substances.				
Elements.				
Fluorine	F	Gas	—187.0	Group II. Irritants. Chap. VIII and IX.
Chlorine	Cl	Gas	— 33.5	
Bromine	Br	Fluid	63.0	
Iodine	I	Solid	148.0	
Ozone	O_3	Gas	—119.0	
Nitrogen	N	Gas	—195.0	Group I. Simple Asphyxiants. Chap. VII.
Helium	He	Gas	—267.0	
Hydrogen	H	Gas	—253.0	
Mercury	Hg	Liquid	357.3	Group IV. Inorganic and organometallic compounds. Chap. XIV.
Phosphorus	P	Solid	290.0	
Acids, Bases, and Oxides.				
Hydrochloric acid	HCl	Gas	— 83.0	Group II. Irritants. Chap. VIII and IX.
Chlorine monoxide	Cl_2O	Gas	— 19.0	
Chlorine dioxide	ClO_2	Gas	10.0	
Hydrofluoric acid	HF	Gas	19.4	
Sulfuric acid	H_2SO_4	Liquid	338.0	
Sulfur dioxide	SO_2	Gas	— 8.0	
Nitrogen dioxide	NO_2 and N_2O_4	Gas	26.0	
Ammonia	NH_3	Gas	— 33.5	
Nitrous oxide	N_2O	Gas	— 87.9	Simple Asphyxiant. Group I.
Carbon dioxide	CO_2	Gas		
Carbon monoxide	CO	Gas	—190.0	Chemical Asphyxiant. Asphyxiants. Chap. VII.

TABLE OF NOXIOUS GASES LISTED ACCORDING TO CHEMICAL COMPOSITION AND CLASSIFIED ACCORDING TO THEIR ACTION.—*Cont.*

Name	Formula	Ordinary Condition	Boiling Point, Degrees Centigrade	Nature of Physiological Action; Classification
Hydric Compounds of Non-Metallic Elements.				
Hydrogen sulfide	H_2S	Gas	— 61.8	Group IV. Inorganic and Organometallic compounds. Chap. XIV.
Hydrogen arsenide	H_3As	Gas	— 55.0	
Hydrogen phosphide	H_3P	Gas	— 85.0	
Salts.				
Phosphorus trichloride	PCl_3	Liquid	76.0	Group II. Irritants. Chap. VIII and IX.
Phosphorus pentachloride	PCl_5	Liquid	160-165	
Arsenic trichloride	$AsCl_3$	Liquid	130.2	
Silicon tetrachloride	$SiCl_4$	Liquid	56.5	Probably resembles carbon tetrachloride.
Organometallic Compounds.				
Diethyl diarsine	$(C_2H_5)_4As_2$	Liquid	190.0	Group IV. Inorganic and organometallic compounds. Chap. XIV.
Cacodyl	$(CH_3)_4As_2$	Liquid	170.0	
Cacodyl oxide	$(CH_3)_4As_2O$	Gas	12.0	
Diethyl mercury	$(C_2H_5)_2Hg$	Liquid	159.0	
Tetraethyl lead	$(C_2H_5)_4Pb$	Liquid		
Nickel carbonyl	$Ni(CO)_4$	Gas		

Hydrocarbons of the Fatty Series.

Methane	CH_4	Gas	— 160.0	Group III. Volatile Drugs and Druglike Substances. Chap. X.-XIII. Lower members simple asphyxiants. Chap. VII. Higher members also irritants. Chap. VIII and IX.
Ethane	C_2H_6	Gas	— 85.4	
Propane	C_3H_8	Gas	— 37.0	
Butane	C_4H_{10}	Gas	1.0	
Pentane	C_5H_{12}	Liquid	37.0	
Hexane	C_6H_{14}	Liquid	69.0	
Heptane	C_7H_{16}	Liquid	98.0	
Octane	C_8H_{18}	Liquid	124.0	
Nonane	C_9H_{20}	Liquid	148.0	
Decane	$C_{10}H_{22}$	Liquid	168.0	

(The low volatility and low solubility of the higher homologues of the series prevent their absorption in quantities sufficient to induce physiological action.)

Ethylene	C_2H_4	Gas	— 103.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII. Lower members of series also simple asphyxiants. Chap. VII.
Propylene	C_3H_6	Gas		
Butylene	C_4H_8	Gas	— 5.0	
Amylene	C_5H_{10}	Liquid	35.0	
Hexylene	C_6H_{12}	Liquid	70.0	
Heptylene	C_7H_{14}	Liquid	100.0	
Acetylene	C_2H_2	Gas		
Allylene	C_3H_4	Gas		
Centonylene	C_4H_6	Gas	18.0	

TABLE OF NOXIOUS GASES LISTED ACCORDING TO CHEMICAL COMPOSITION AND CLASSIFIED ACCORDING TO THEIR ACTION.—*Cont.*

Name	Formula	Ordinary Condition	Boiling Point, Degrees Centigrade	Nature of Physiological Action; Classification
Hydrocarbons of the Aromatic Series.				
Benzene	C_6H_6	Liquid	81.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
Toluene	C_7H_8	Liquid	111.0	
Xylene	C_8H_{10}	Liquid	140.0	
Alcohols.				
Methyl alcohol	CH_3OH	Liquid	66.0	
Ethyl alcohol	C_2H_5OH	Liquid	78 5	
Propyl alcohol	C_3H_7OH	Liquid	97.5	
Butyl alcohol	C_4H_9OH	Liquid	117.0	
Amyl alcohol	$C_5H_{11}OH$	Liquid	137.0	
Ethers.				
Methyl ether	CH_3OCH_3	Gas	— 21.0	
Ethyl ether	$C_2H_5OC_2H_5$	Liquid	35.0	
Propyl ether	$C_3H_7OC_3H_7$	Liquid	86.0	
Ketones				
Dimethyl ketone (acetone)	$(CH_3)_2CO$	Liquid	65.5	
Methyl ethyl ketone	$CH_3COC_2H_5$	Liquid	81.0	

Aldehydes.

Formaldehyde	CH_2O	Gas	— 21.0	Group II. Irritants. Chap. VIII and IX, but also Volatile Drugs and Druglike Substances. Chap. X-XIII.
Acetaldehyde	C_2H_4O	Liquid	20.8	
Propylaldehyde	C_3H_6O	Liquid	49.0	
Butaldehyde	C_4H_8O	Liquid	74.0	
Acraldehyde (acrolein)	C_3H_4O	Liquid	52.0	

Halogen Derivatives of the Fatty Hydrocarbons.

Methyl chloride	CH_3Cl	Gas	— 24.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
Methyl bromide	CH_3Br	Gas	4.5	
Methyl iodide	CH_3I	Liquid	44.0	
Ethyl chloride	C_2H_5Cl	Gas	12.5	
Ethyl bromide	C_2H_5Br	Liquid	39.0	
Ethyl iodide	C_2H_5I	Liquid	72.0	
Methylene dichloride	CH_2Cl_2	Liquid	41.0	
Dichloroethylene	$C_2H_2Cl_2$	Liquid	55.0	
Ethylene dichloride	$C_2H_4Cl_2$	Liquid	85.0	
Trichloromethane	$CHCl_3$	Liquid	61.2	
Tribromomethane	$CHBr_3$	Liquid	151.2	
Trichloroethylene	$CHClCCl_2$	Liquid	87.1	
Trichloroethane	$CHCl_2CH_2Cl$	Liquid	115.0	
Tetrachloromethane	CCl_4	Liquid	76.7	
Perchloroethylene	C_2Cl_4	Liquid	119.0	
Tetrachloroethane	$CHCl_2CHCl_2$	Liquid	147.2	
Pentachloroethane	CCl_3CHCl_2	Liquid	161.7	

Halogen Derivatives of the Aromatic Series.

Chlorobenzene	C_6H_5Cl	Liquid	132.0	Group II. Irritants. Chap. VIII and IX.
Bromobenzene	C_6H_5Br	Liquid	155.0	
Chlorotoluene	C_7H_7Cl	Liquid	150-160	
Benzyl chloride	C_7H_7Cl	Liquid	176.0	

TABLE OF NOXIOUS GASES LISTED ACCORDING TO CHEMICAL COMPOSITION AND CLASSIFIED ACCORDING TO THEIR ACTION.—*Cont.*

Name	Formula	State at Ordinary Condition	Boiling Point, Degrees Centigrade	Nature of Physiological Action; Classification
Sulfur Derivatives of the Hydrocarbons.				
Dimethyl sulfate	$(CH_3)_2SO_4$	Liquid	188.0	Group II. Irritants. Chap. VIII and IX.
Dichlorethyl sulfide	$(CH_2ClCH_2)_2S$	Liquid		
Thiophene	C_4H_4S	Liquid	84.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
Carbon disulfide	CS_2	Liquid	46.2	
Ethereal Salts of Organic Acids.				
Methyl formate	CH_3CO_2H	Liquid	32.3	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
Methyl acetate	$CH_3CO_2CH_3$	Liquid	57.5	
Methyl butanate	$CH_3CO_2C_3H_7$	Liquid	102.2	
Ethyl formate	$C_2H_5CO_2H$	Liquid	54.4	
Ethyl acetate	$C_2H_5CO_2CH_3$	Liquid	77.0	
Ethyl butanate	$C_2H_5CO_2C_3H_7$	Liquid	119.0	
Propyl acetate (Iso.)	$C_3H_7CO_2CH_3$	Liquid	35.8	
Butyl acetate (Iso.)	$C_4H_9CO_2CH_3$	Liquid	116.3	
Amyl acetate	$C_5H_{11}CO_2CH_3$	Liquid	148.0	

Nitrates and Nitrites of the Hydrocarbons.

Methyl nitrate	CH_3NO_3	Liquid	66.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
Ethyl nitrate	$C_2H_5NO_3$	Liquid	87.0	
Ethyl nitrite	$C_2H_5NO_2$	Gas	17.0	
Propyl nitrite	$C_3H_7NO_2$	Liquid		
Butyl nitrite	$C_4H_9NO_2$	Liquid		
Amyl nitrite	$C_5H_{11}NO_2$	Liquid	99.0	

Nitro Compounds.

Nitromethane	CH_3NO_2	Liquid	100.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
Nitroethane	$C_2H_5NO_2$	Liquid	114.0	
Nitrobenzene	$C_6H_5NO_2$	Liquid	205.0	

Amines.

Methylamine	CH_3NH_2	Gas	— 6.0	Group II. Irritants. Chap. VIII and IX. Also, Volatile Drugs and Druglike Substances. Chap. X-XIII.
Dimethylamine	$(CH_3)_2NH$	Gas	8-9	
Trimethylamine	$(CH_3)_3N$	Gas	3.5	
Ethylamine	$C_2H_5NH_2$	Gas	18.7	
Diethylamine	$(C_2H_5)_2NH$	Liquid	56.0	
Triethylamine	$(C_2H_5)_3N$	Liquid	89.0	
Benzylamine	$C_6H_5CH_2NH_2$	Liquid	185.0	

Amido Compounds.

Aniline	$C_6H_5NH_2$	Liquid	183.0	Group III. Volatile Drugs and Druglike Substances. Chap. X-XIII.
O-m toluidine	$C_6H_4CH_3NH_2$	Liquid	197.0	
Methylaniline	$C_6H_5NHCH_3$	Liquid	191.0	
Dimethylaniline	$C_6H_5N(CH_3)_2$	Liquid	192.0	

TABLE OF NOXIOUS GASEA LISTED ACCORDING TO CHEMICAL COMPOSITION AND CLASSIFIED ACCORDING TO THEIR ACTION.—*Cont.*

Name	Formula	Ordinary Condition	Boiling Point, Degrees Centigrade	Nature of Physiological Action; Classification
Pyridine and Turpentine.				
Pyridine	C_5H_5N	Liquid	115.0	Group II. Irritants. Chap. VIII and IX.
Turpentine	$C_{10}H_{16}$	Liquid	116.7	
Cyanogen Compounds.				
Cyanogen	C_2N_2	Gas	— 34.4	Group I. Asphyxiants. Chap. VII.
Cyanogen chloride	CNCl	Gas	15.5	
Hydrocyanic acid	HCN	Gas	26.0	
Acetonitrile	CH_3CN	Liquid	81.0	
Propionitrile	C_2H_5CN	Liquid	97.0	
Methyl isonitrile	CH_3NC	Liquid	58.0	
Ethyl isonitrile	C_2H_5NC	Liquid	82.0	
Benzonitrile	C_6H_5CN	Liquid	190.0	
Methyl mustard oil	CH_3NCS	Liquid	119.0	Group II. Irritants. Chap. VIII and IX.
Ethyl mustard oil	C_2H_5NCS	Liquid	133.0	
Allyl mustard oil	C_3H_5NCS	Liquid	150.7	

Group 1. Asphyxiants. This group includes volatile substances which induce anoxemia or an equivalent condition, in that they interfere with the supply or utilization of oxygen in the body. It is characteristic of such gases that they bring about this result without any direct interference with the mechanics of respiration. They do no direct injury to the lungs.

This group is further subdivided: (a) Simple Asphyxiants. These are inert gases, that is inert physiologically, altho they may be from the standpoint of chemistry quite active substances. They act by excluding oxygen from the lungs. (b) Chemical Asphyxiants. These are gases which possess some specific property which renders them asphyxiants even when they are present in very minute amounts in the air. Their action is therefore not that of excluding oxygen from the lungs. They exert either an action upon the blood which prevents it from transporting oxygen, altho the lungs are well aërated, or upon the tissues to prevent them from using oxygen, altho it may be brought to them in ample amount by the blood.

Group 2. Irritants. The gases of this class are for the most part substances which from the standpoint of chemistry would be regarded as corrosive. They injure the surface tissues of the respiratory tract and thus induce inflammation of the air tubes and of the lungs themselves. While the effects of the different irritant gases differ considerably one from another, these differences depend chiefly upon the solubilities of the substances and on this basis gases of this class are more easily arranged in a scale than in a succession of subclasses.

Group 3. Volatile Drugs and Druglike Substances. This group includes those gases which exert a druglike action after they have been absorbed thru the lungs into the blood. They consist of hydrocarbons, largely (a) anesthetics but including also (b) organic nitro compounds. These nitro compounds may be further subdivided into those whose predominant action is the alteration and destruction of hemoglobin, and those which, like amyl nitrite, dilate the blood vessels and thus exhibit the so-called nitrite effect.

Group 4. Inorganic and Organo-Metallic Cases. The gases and vapors containing phosphorus, mercury, lead, and so on, are not asphyxiants or pulmonary irritants (at least in their chief action), but are true poisons acting only after absorption into the blood. They are volatile poisons in the strictly toxicological sense. Each has its own specific physiological action.

Chapter VII.

Group I. Asphyxiants.

Two Types of Asphyxia. There are two types of asphyxia: (1) asphyxia caused by the cessation of breathing, and (2) asphyxia caused in some other way and without cessation of breathing, except as a terminal event. The distinction between these two types lies in the presence in the first of an excess of carbon dioxide in the body. The second consists wholly in deficiency of oxygen.

The first of these forms of asphyxia occurs when breathing is stopped either mechanically or by the action of a drug upon the respiratory center; the blood then fails to obtain oxygen from the air. This may be due to obstruction of the windpipe or other form of strangulation, or to drowning. It may result from the action of some drug such as morphine or chloroform, which causes a cessation of the respiratory movements. However it may be caused, there is not only a deprivation of oxygen, but an almost equally significant cessation of elimination of carbon dioxide. As the anoxemia develops the carbon dioxide also accumulates; and both conditions exert effects on the body.

On the other hand, in asphyxia of the second type caused, for example, by the inhalation of a high concentration of nitrogen, the tissues of the body are primarily merely deprived of oxygen. In such asphyxiation the elimination of carbon dioxide is not interfered with; the anoxemia alone exerts a direct action on the body. As a secondary effect this form of asphyxia may even involve such excessive breathing that the content of carbon dioxide in the body is also greatly depleted. Thus to anoxemia is added acapnia. Asphyxia of the first type is the common cause of death from noxious gases which are not classified as asphyxiants, but which as part of their drug action abolish respiration. Asphyxia of the second type is the characteristic effect of the group of gases and vapors which are properly termed asphyxiants.

Anoxemia from Incarceration.

Asphyxia resulting from incarceration in an air-tight enclosure, such as the safe deposit vault of a bank, is rare, but the question of the length of time that a man can exist under such circumstances is

sometimes important. The answer can be readily calculated from the data on respiration given in Chapter II. A point to be emphasized, however, is the fact that few structures other than metal vaults are actually air-tight. The plastered walls of the ordinary room admit air with sufficient freedom to keep the oxygen from being appreciably diminished. The same is true of concrete walls. The vitiation of room air by the breathing of the occupants does not ordinarily depend upon the alteration in the composition of the air, but upon its change in physical character, particularly its temperature, humidity and movement.

The length of time that a man can remain in an air-tight enclosure without suffering seriously from anoxemia depends upon the volume of oxygen consumed and the volume of air present. At rest the average man consumes from 0.2 to 0.3 liter of oxygen per minute; under exercise he consumes much more. During rest about 7 hours are required to reduce the oxygen in one cubic meter of air to one-half its normal content. At about this degree of depletion, altho no sharp line can be drawn, serious discomfort and even danger may be considered to develop.

Symptoms of Asphyxia.

Nervous tissue is more sensitive to deprivation of oxygen than is any other tissue. Anoxemia of mild degree impairs its coördination. Even a short duration of asphyxia abolishes its functional activity. Complete anoxemia maintained even for 10 minutes, or less acute for a longer time, may lead to irreparable damage to the nervous system.

The symptoms of asphyxia arise from the derangement of the nervous system. The course of the symptoms depends upon the degree and duration of the anoxemia. In severe asphyxia such, for example, as follows the inhalation of pure nitrogen, or of a high concentration of hydrocyanic acid gas, unconsciousness develops at once; the man falls as tho struck down by a blow on the head. If the asphyxia continues he dies within a few minutes. Asphyxia of gradual development and progressive severity is well illustrated by the effects of inhalation of low concentrations of carbon monoxide. The symptoms arise from the anoxemia and pass thru a succession of phases, ranging from the first perceptible derangement of function to death. Even in mild but uniformly maintained asphyxia such as that resulting, for example, from the inhalation of air diluted with a moderately high, but not immediately fatal, concentration of nitrogen, the symptoms first produced by the anoxemia become progressively more severe. This fact indicates that the derangement of the nervous system is

influenced, not only by the severity of the anoxemia, but to a no less important degree also by its duration.

When asphyxiation develops sufficiently slowly to allow the symptoms to appear in their full series, they present the following succession of clinical pictures:

First Stage of Anoxemia. When the oxygen of the inspired air is diminished from the normal 21 per cent, about 160 mm., to values between 16 and 12 per cent, that is, somewhat beyond the point at which a candle is extinguished, the first perceptible signs of anoxemia develop. The volume of breathing is increased and the pulse rate is accelerated. (Both of these conditions actually begin earlier, but not noticeably.) The ability to maintain attention and to think clearly is diminished but can be restored with effort. Muscular coördination for the finer skilled movements, such as writing, is somewhat disturbed. Respiration is much increased, so that the amount of carbon dioxide in the body is correspondingly decreased.

Second Stage of Anoxemia. When the oxygen is diminished to values between 14 and 9 per cent, the higher centers of the brain are affected. Consciousness continues but the judgment becomes faulty. Severe injuries such as burns, bruises and even broken bones, may cause no pain. Emotions, particularly ill temper and pugnacity, and less often hilarity, or an alternation of moods, are aroused with abnormal readiness. Muscular efforts lead to rapid fatigue, and may permanently injure the heart. As they intensify the anoxemia, they may induce fainting. The respiration is frequently of the intermittent or Cheyne-Stokes type.

Third Stage of Anoxemia. When the oxygen is diminished to values between 10 and 6 per cent, nausea and vomiting may appear. The subject loses the ability to perform any vigorous muscular movements. Bewilderment and loss of consciousness follow, either with fainting, or in a rigid glassy-eyed coma. If revived the subject may have no recollection of this stage, or an entirely erroneous belief as to what has happened.

Up to this stage, or even in it, he may be wholly unaware that anything is wrong. Then his legs give way, leaving him unable to stand or walk. This is often the first and only warning, and it comes too late. He may realize that he is dying, but he does not greatly care. It is all quite painless.

Fourth Stage of Anoxemia. When the oxygen is diminished below 6 per cent, respiration consists of gasps. Convulsive movements may occur. Then the breathing stops, but the heart continues to beat for 6 to 8 minutes. Then death.

Sequelae of Anoxemia.

If the asphyxia is stopped before the fourth stage, most of the symptoms clear up in a short time. The most frequent after-effect of anoxemia is a headache, often associated with nausea and general malaise, which may increase in intensity for several hours and last even until the next day. This post-asphyxial headache is due to the edematous condition which develops in the tissues of the brain and produces an increased intercranial pressure. The intravenous administration of hypertonic saline tends to withdraw the excess of water from the brain and thus to relieve the edema.

In some cases in which the anoxemia has been both severe and prolonged, organic changes of a degenerative type subsequently develop in the nervous tissue. Cases of this type include a variety of paralyses, amnesias and other nervous derangements, with rare (alleged) cases of degeneration in other organs. The number of cases in which organic changes, even in the brain, result from asphyxia is small in comparison to the number of persons who are severely asphyxiated. The large majority of such sequelae are due to asphyxia from inhaling carbon monoxide. This is not due to any special action of carbon monoxide upon nerves, for it has none; it is due to the prolonged subfatal asphyxia which this gas frequently induces.

Pulmonary changes are common after prolonged and severe asphyxia. Clinically these changes are indicated by râles and areas of dullness; in fatal cases extensive areas of congestion are found in the lungs. These pulmonary changes are probably due to alterations in the circulation, and not to any direct action upon the lungs. Pneumonia is a frequent sequel of prolonged asphyxia, and is incited by the chilling incident to exposure during the period of unconsciousness, by the aspiration of mucus and saliva, and by the pulmonary changes above noted. The asphyxiants, with the sole exception of cyanogen chloride, have no direct irritant action upon the tissues of the respiratory tract.

Symptoms Resulting from Chronic Anoxemia.

The reaction of the body to chronic anoxemia depends upon the duration and uniformity of the periods of oxygen deficiency. Prolonged slight anoxemia, such as results from change of residence or an expedition to a high altitude, leads to a definite series of compensatory changes classed together under the term acclimatization. The number of red cells in the blood is increased, first by a merely relative change due to the abstraction of water from the blood, and second, and more slowly, by a greater production of red cells. The first process occurs in a few hours; the second requires weeks or months. The polycythemia increases the amount of oxygen which the blood can carry.

The breathing is somewhat increased in volume as a result of the anoxemia. In some persons this occurs in a few hours, in others in a few minutes, in others again only in the course of some days. This increase of pulmonary ventilation lowers the pressure of carbon dioxide in the blood and displaces the normal balance of alkali and carbonic acid, and consequently the hydrogen ion concentration, so that the blood becomes abnormally alkaline. A complex of symptoms develops as a result of the condition of anoxemia and its consequent acapnia. This "mountain sickness" is characterized by depression, nausea, headache and malaise. Continuation of the anoxemia and its accompanying acapnia results in a diminution of the alkali of the blood to balance the diminished carbonic acid; and a normal hydrogen ion concentration is thus restored. The increased volume of respiration is then maintained in this new adjustment by the same processes as at sea level. After a variable period from one or two days up to a week or two weeks of continued anoxemia, the symptoms of mountain sickness pass off and acclimatization is established. In fully acclimatized individuals the increase of volume of breathing and of red cells in the blood, the diminution of alkali in the blood, and of carbon dioxide in the alveolar air are all proportional to the altitude. In these effects of barometric pressure the oxygen partial pressure is the essential factor. Each altitude from sea level to 14,000 feet has its own nicely adjusted degree of functional readjustment, and this holds true also, altho with increasing strain upon the system, up to 23,000 feet. Owing to the necessity for an increased volume of respiration, muscular exertion becomes increasingly difficult as the altitude increases, even for those who are fully acclimatized; for if a certain exertion increases respiration from 7 liters at rest to 28 at sea level, it increases in an acclimatized man, for example, from 14 liters during rest to 56 when he makes the same exertion.

When the periods of anoxemia are irregular and relatively brief, as for example occurs in repeated aëroplane flights to great altitudes, the mechanism of compensation is alternately started and reversed. Under these conditions acclimatization does not occur. Instead an ill defined condition of nervousness, irritability, and weakness results which is designated as "air staleness" and is similar to the state known to athletes as "overtraining" or "out of condition."

Daily exposure to carbon monoxide in small amounts may lead to either of the types of response here described. Workers about blast furnaces and in some automobile repair shops, where there is almost constant exposure to carbon monoxide develop a considerable degree of true acclimatization, as indicated by an increase in the red cell count.

On the other hand, when, as is generally the case, the exposure is less regular, symptoms of air staleness may develop.

Treatment of Asphyxia.[1]

The treatment of asphyxia, as outlined here, was developed primarily to deal with asphyxia caused by carbon monoxide—the commonest of all forms of poisoning by gases. The treatment, however, is applicable without modification to all the other asphyxiants. It is indeed the general treatment used for acute poisoning for all noxious gases and vapors which cause failure of respiration. It thus applies equally well to the anesthetic hydrocarbons and hydrogen sulphide. Additional details of procedure applicable to poisoning by some other gases and vapors are noted in the discussion of the particular substances.

The first step in the treatment of asphyxia is to remove the man immediately to fresh but not cold air. He is laid on his stomach, with his face turned to one side. If he is breathing he is given an inhalation of oxygen containing 5 per cent of carbon dioxide. If he is not breathing manual artificial respiration is started at once, and the inhalation of oxygen plus carbon dioxide is administered meanwhile. The inhalation of oxygen and carbon dioxide is continued for 15 to 30 minutes after spontaneous respiration commences. The after treatment consists of general measures designed to prevent the development of pneumonia. Drugs have little value in the treatment of asphyxia. Alcohol is contraindicated.

The points to be clearly understood in connection with the treatment of asphyxia are that the essential condition consists, not in cessation of breathing, for respiration continues almost to death; but in the interruption of the supply of oxygen to the tissues of the body, and especially to the brain. In this respect asphyxia by gases contrasts with drowning and electric shock. In both of those conditions spontaneous respiration is stopped, and artificial respiration is the supremely important measure of assistance. Inhalation of oxygen and carbon dioxide is then merely a useful accessory. After a prolonged severe asphyxia, on the contrary, the victim, unless irretrievable, is generally breathing spontaneously, altho poorly. The administration of oxygen alone is not very effective, for the reason that it is not inhaled in sufficient volume. The carbon dioxide mixed with the oxygen acts, however, as a powerful respiratory and cardiac stimulant. It both replaces the carbon dioxide that the body has lost, and by the increase of respiration induces a deep and full inhalation of the oxygen with which the carbon dioxide is mixed.

Drugs which stimulate respiration when administered hypodermi-

[1] For full details and directions see Chapter XV.

cally are inadvisable because they do not replace, but may even further deplete the body's needed supply of carbon dioxide. Hypodermic medication is of no value, but rather the contrary, in this field.

Two Subgroups of Asphyxiants.

Asphyxiants as here defined are substances which induce anoxemia thru some means other than interference with the mechanics of respiration. They do not directly interfere with breathing. They merely make it ineffective as a means of obtaining oxygen. There are two subgroups of this class of gases: simple asphyxiants and chemical asphyxiants. The simple asphyxiants are inert physiologically and act only in high concentration. They induce asphyxia by the exclusion of oxygen from the lungs; but without being themselves absorbed into the blood. Chemical asphyxiants are substances which, after they have been absorbed into the blood, exert some specific effect upon the blood or tissues. Thus such a chemical asphyxiant may prevent oxygen from reaching the tissues, altho oxygen is present in ample quantity in the lungs. Or, it may leave the blood virtually unaffected but prevent the tissues from using the oxygen which the blood may bring to them in normal amounts. The important practical distinction between the simple asphyxiants and the chemical asphyxiants is that minute amounts of the latter are highly poisonous.

Simple Asphyxiants. The simple asphyxiants are numerous. This subgroup of substances includes two types. Those of one type are entirely inert physiologically; they are such gases as hydrogen and nitrogen. Those of the other type have some slight specific action, but when they are inhaled in high concentration with air they cause asphyxia before this action is manifest. The simple asphyxiants belonging to the latter type of this subgroup include the lighter hydrocarbons of the aliphatic series such as methane and ethane, and some of the gases which, when administered with oxygen, are now used as anesthetics.

The simple asphyxiants act entirely by excluding oxygen from the lungs; their effect is proportional to the extent to which their presence diminishes the percentage, or rather pressure, of oxygen in the inspired air. They all act identically, therefore, when present in equal molecular concentration. Moreover they must be present in considerable amounts before they exert any appreciable effect. In the sections describing the symptoms of anoxemia it was stated that the oxygen can be reduced to two-thirds of its normal percentage in the air before noticeable symptoms of anoxemia develop. A reduction of the oxygen to this degree necessitates the presence of the simple asphyxiants in a concentration of 33 per cent in the mixture of air and gas. When the

SIMPLE ASPHYXIANTS.

Name	Formula	Boiling Point, ° C.	Occurrence
Nitrogen	N	—195.0	Constituent of "black damp" found in mines (87 per cent. nitrogen, 13 per cent. carbon dioxide).
Hydrogen *	H	—253.0	Used for filling balloons.
Helium	He	—267.0	
Methane	CH_4	—160.0	Marsh gas—"fire damp" of mines. (Explosive.)
Ethane	C_2H_6	— 85.4	For description see Anesthetic Hydrocarbons. Chapters X and XI. These substances have anesthetic properties when administered with oxygen, but when mixed with air act chiefly as simple asphyxiants.
Propane	C_3H_8	— 37.0	
Nitrous Oxide	N_2O	— 87.9	
Ethylene	C_2H_4	—103.0	
Acetylene	C_2H_2	....	

* See Chapter XIV for occurrence of hydrogen arsenide in hydrogen used for filling balloons.

gas is present to the extent of 50 per cent, a man is soon rendered incapable of making a vigorous effort to escape. About 75 per cent is quickly fatal.

Chemical Asphyxiants. The chemical asphyxiants are few in number; only two substances can be thus classified: carbon monoxide and cyanide in its various compounds. Nevertheless, owing to the frequency of asphyxia by carbon monoxide, this group is by far the most important among all the classes of noxious gases. Carbon monoxide is an asphyxiant thru its property of combining with the hemoglobin of the blood to the exclusion of oxygen. Cyanides, on the other hand, act upon the tissues and temporarily deprive them of the capacity to use the oxygen which the blood brings to them. In their points of action carbon monoxide and cyanide in its various volatile forms offer an interesting contrast to the gases which act merely as simple asphyxiants. The latter exert their action in the lungs by keeping oxygen from reaching the blood. Carbon monoxide exerts its action in the blood itself. Oxygen is brought in contact with the blood in the lungs in ample quantity at all times during most cases of carbon monoxide asphyxia, but the blood cannot absorb or transport it. Cyanide neither prevents oxygen from reaching the blood nor from being absorbed into the blood and transported by it. It acts in the tissues and prevents them from using the oxygen which reaches them.

Carbon Monoxide.

Carbon monoxide, CO, is a gas at ordinary temperatures. It has a slight garliclike odor, but this is seldom noticed. Its boiling point is — 190°C. and its specific gravity, compared to air, is 0.967. At 40°C. its solubility in water by volume is 0.0178.

Only in rare conditions does carbon monoxide appear in nature; it is, however, almost universally present wherever man lives and works. It usually originates from the incomplete combustion of carbonaceous material. Illuminating gas is one of the commonest sources of acute poisoning; many of these cases are suicidal. Coal gas, which is made by the destructive distillation of coal, contains from 4 to 6 per cent of carbon monoxide. Water gas, which is made by passing steam over heated coke, contains about 40 per cent of carbon monoxide. In England and the European continent coal gas is chiefly used for illuminating gas. In American cities a mixture is usually supplied consisting largely of water gas enriched either with some coal gas or petroleum products to afford luminosity and raise the thermal value. Illuminating gas in the United States contains from 6 to 30 per cent or even more of carbon monoxide; generally it is between 20 and 30 per cent.

Gas which is mixed with air before being burned shows only a blue flame. Practically all the carbon monoxide which it contains is consumed, producing carbon dioxide. If, however, the blue flame is brought near a cold body, such as a water pipe or cooking utensil, it is chilled, and as a result not only may the carbon monoxide in the gas escape combustion, but carbon monoxide may even be produced from other carbonaceous gases. In fact such a production of carbon monoxide readily occurs even from natural gas, which is chiefly methane and contains no carbon monoxide, when it is used in water heaters and in improperly arranged open gas fires in living rooms. A similar result is produced when the burner is lighted improperly or "snaps back" and burns at the base. When fatalities occur from a production of carbon monoxide in one of these ways the claim is sometimes made that the death was not caused by carbon monoxide, since no gas leak occurred; and that it must have been due to the consumption of all the oxygen in the room and to excess of carbon dioxide. But in fact low oxygen would extinguish the fire long before it would seriously affect a man, and excess of carbon dioxide up to 10 or 12 per cent would merely stimulate respiration.

The gas from blast furnaces contains from 24 to 30 per cent of carbon monoxide; producer gas from 22 to 26 per cent. The smoke from a coal fire contains variable amounts of carbon monoxide, depend-

ing upon how free the draft is; the more the combustion is impeded the higher is the percentage of carbon monoxide. Flue gas from boilers and house heaters has sometimes caused poisoning thru leaks in the heating apparatus or from the smoke or fumes after leaving the flue. The gas from charcoal braziers and from coke-burning salamanders contains considerable quantities of carbon monoxide; when used without flues they frequently give rise to poisoning. The smoke in burning buildings, particularly if the fire is of the smouldering basement type, contains a considerable percentage of carbon monoxide; and poisoning by the smoke is mainly due to carbon monoxide. Fires in mines produce especially high percentages of carbon monoxide because of the confined space and deficiency of oxygen. The "after damp" produced by an explosion of coal dust, the cause of many deaths, also owes its toxicity to carbon monoxide.

The exhaust gas from internal combustion engines contains carbon monoxide in percentages ranging from a fraction of 1 per cent to 7 per cent or even higher. The variation depends upon the proportion of air and gasoline in the mixture burned; the carbon monoxide increases with increase in the proportion of gasoline, that is with a rich mixture. A rough estimate of the volume of carbon monoxide that an automobile may produce is one cubic foot (28 liters) per minute per 20 horse power. This is sufficient to render the atmosphere of a single car garage deadly within 5 minutes, if the engine is run while the garage doors are closed. As explained above, a man breathing such an atmosphere often falls helpless before he realizes that he is affected. Hence many fatalities. In streets where traffic is congested the content of carbon monoxide rises to about 100 parts per million of air, enough to cause slight headache after long exposure.

Formation of Carbon Monoxide Hemoglobin. Carbon monoxide is, except for one reaction, a physiologically inert gas; it combines with the hemoglobin of the blood to the exclusion of oxygen. Were it not for this one reaction carbon monoxide would be classed with nitrogen and hydrogen as a simple asphyxiant. Animals which have no hemoglobin are quite normal in 80 per cent carbon monoxide and 20 per cent oxygen. Nerve cells of the chick in a drop of serum grow normally in such an atmosphere. A mouse can tolerate a high percentage of carbon monoxide if the pressure of oxygen is also increased. The amount of oxygen which then enters the blood in simple solution eliminates the need for transportation by hemoglobin. All of the toxic action of carbon monoxide, therefore, is exercised thru the anoxemia resulting from the conversion of oxyhemoglobin to carbon monoxide hemoglobin, and the resulting asphyxia.

The reaction between oxygen, carbon monoxide and hemoglobin is reversible, as expressed by the following equation in which hemoglobin is designated by the symbol Hb:

$$HbO_2 + CO \rightleftarrows HbCO + O_2$$

Carbon monoxide displaces oxygen from hemoglobin, and in turn oxygen may displace carbon monoxide from its combination. Red corpuscles, in which the hemoglobin has been joined to carbon monoxide and then freed from the combination by means of oxygen, are not injured; they are as capable of transporting oxygen as if they had never been exposed to the other gas. But so long as the combination with carbon monoxide continues they are incapable of fulfilling their respiratory function.

Carbon monoxide has a greater affinity for hemoglobin than has oxygen; the relative attractions are approximately 300 to 1. The relative amounts of oxygen and carbon monoxide in the air breathed determine the proportions in which the hemoglobin is distributed between the two gases. Thus when the concentration of oxygen is 300 times as high as that of carbon monoxide (0.07 per cent of carbon monoxide in atmospheric air) half of the hemoglobin is converted to the carbon monoxide compound and half retains its oxygen. The distribution is expressed more generally in the following equation:

$$\text{Per cent HbCO formed} = \frac{Pco \times 300}{Po_2 + (Pco \times 300)}$$

Pco and Po_2 are respectively the partial pressures or proportions of carbon monoxide and of oxygen in the air to which the blood is exposed.

According to Stadie and Martin[2] an increase of carbon dioxide in the blood decreases the affinity of hemoglobin for carbon monoxide as compared with its affinity for oxygen. Thus increase of carbon dioxide (acting thru a decrease of pH) tends, under otherwise similar conditions, to eliminate the monoxide from the blood. Presumably the loss of carbon dioxide which occurs during the excessive breathing while asphyxia is developing tends to increase the relative force of attraction of hemoglobin for carbon monoxide in comparison to oxygen.

Volume of Breathing as Limiting Factor in Rate of Absorption. When blood is exposed to 0.07 per cent of carbon monoxide in air, by shaking vigorously a small volume of blood in a bottle with a large volume of air, approximately half of the hemoglobin is combined with the gas, and oxygen is excluded to that extent. But when an atmosphere of 0.07 per cent of carbon monoxide in air is breathed,

[2] Stadie and Martin, Journal of Clinical Research, 1925, II, p. 77.

many hours are required to approximate this distribution of the hemoglobin in the blood in the body. Many days of exposure would be required theoretically before the final equilibrium was attained. The rate of absorption of carbon monoxide by the lungs cannot exceed the amount of the gas drawn in by the breathing. Thus the volume of respiration is a limiting factor in the rate at which carbon monoxide hemoglobin can be formed.

This limitation on rate of absorption will be rendered clearer by an example: The average man at rest has a pulmonary ventilation of approximately 5 liters of air per minute. This assumes a volume of respiration of 7.5 liters a minute and a dead space of 33 per cent. Now 5 liters of air holding 0.07 per cent of carbon monoxide would represent 0.0035 liter (3.5 cc.) of the gas, so that 0.21 liter ($3.5 \times 60 =$ 210 cc.) at most would come in contact with the blood during the course of one hour. The total volume of blood in the body of an average adult is about 5 liters and has the capacity to hold approximately 1.0 liter of oxygen. Each thousandth of a liter of carbon monoxide that is absorbed into the blood decreases the oxygen capacity by an equivalent amount, that is by 0.1 per cent. At the end of one hour the maximum amount by which, under these conditions, the oxygen capacity can be replaced by carbon monoxide would be 21 per cent; an amount sufficient to elicit only slight symptoms of anoxemia. In reality somewhat less than the amount of carbon monoxide thus estimated would be combined in the blood, for as the absorption continues the rate falls farther and farther short of total absorption. The reason is that, as the reaction approaches equilibrium, the balance of pressure between the oxygen and carbon monoxide in the blood, and of their attractions for hemoglobin shifts automatically and progressively until at equilibrium carbon monoxide is displaced by oxygen in amount each minute equal to that in which oxygen is displaced by carbon monoxide.

When the volume of breathing is increased by muscular exertion, the absorption of carbon monoxide is proportionally accelerated. The equilibrium percentage saturation with carbon monoxide is the same as at rest, but it is approached more rapidly. A rough, but useful rule is that one-half the carbon monoxide inhaled is absorbed during the early stages of exposure. (By "inhaled" is meant here the total volume of respiration per minute and not only the pulmonary ventilation, which is the volume of respiration minus the allowance for dead space.)

When two individuals, one of whom is much larger than the other, or when an adult and a child, both at rest, are exposed to the same atmosphere, it is the smaller and younger, the individual with the more active metabolism, who absorbs carbon monoxide and tends to approach saturation the more rapidly. In such cases it is the relation of the

volume of respiration to the size of the body and its volume of blood which influences the rate at which oxygen is displaced by carbon monoxide. In the resting state the volume of breathing varies between individuals as a function of the surface area of their bodies; the volume of blood on the other hand varies as the weight of the body. In bodies of the same shape, whether spheres, cubes or human bodies, the less the bulk the greater the relative surface. Small individuals therefore succumb to carbon monoxide more rapidly than large individuals, for the volume of their respiration is greater in relation to their volume of blood. This comparison finds its extreme expression, and a very practical application, in the rate of saturation as between men on the one hand and such small animals as the mouse and canary on the other. In mine rescue operations the animals are carried into vitiated air as indicators of the presence of carbon monoxide. When the mouse can no longer maintain its equilibrium, or the canary falls off its perch, experience proves that men breathing the same atmosphere may estimate the time for their escape; for as men have only about one-twentieth the skin surface of the small animal per unit of body weight, so twenty times as long a stay in the atmosphere will bring them into the same condition as the canary and the mouse.

Effects of Various Degrees of Saturation. The symptoms resulting from the inhalation of carbon monoxide depend upon the degree of anoxemia, that is the extent of combination of the hemoglobin with the gas. The following table gives the average physiological response to various percentages of saturation of the hemoglobin with carbon monoxide.

PERCENTAGE SATURATION OF THE BLOOD WITH CARBON MONOXIDE AND CORRESPONDING PHYSIOLOGICAL EFFECTS.

Per Cent. of Hemoglobin in Combination with Carbon Monoxide	Physiological Effect
10	No appreciable effect except shortness of breath on vigorous muscular exertion.
20	No appreciable effect in most cases except short wind even on moderate exertion; slight headache in some cases.
30	Decided headache; irritable; easily fatigued; judgment disturbed.
40–50	Headache, confusion, collapse and fainting on exertion.
60–70	Unconsciousness; respiratory failure and death if exposure is long continued.
80	Rapidly fatal.
Over 80	Immediately fatal.

Elimination of Carbon Monoxide from the Body. The anoxemia induced by carbon monoxide does not, as in the case of the simple asphyxiants, cease as soon as fresh air is inhaled, but persists in diminishing degree during the period of elimination. Even with the simple asphyxiants the after-effects of anoxemia persist for some time after an ample supply of oxygen is restored. With carbon monoxide there is the additional disadvantage that the period of anoxemia is often much longer than the period of actual exposure in the atmosphere containing the gas. Carbon monoxide is not burned to carbon dioxide nor otherwise destroyed in the body, but is eliminated thru the lungs when air free from carbon monoxide is inhaled. The mechanism is the reverse of that of absorption. It does not separate from hemoglobin spontaneously, but is displaced by the pressure and mass action of oxygen. During the first hour after moderate degrees of gassing, one-half, or a little more of the gas that has been absorbed is eliminated under ordinary circumstances; complete elimination under the action of fresh air is not effected for many hours, however. After brief exposure to a high concentration of the gas with rapid absorption, the anoxemia is therefore suffered mainly during the period of elimination. It is extremely important to hasten the elimination by the inhalation of oxygen and 5 per cent carbon dioxide, as described above, and thus to terminate the asphyxia. This is demonstrated by the fact that of two workmen exposed for a short time to a high concentration of carbon monoxide and equally gassed, one who is allowed to recover spontaneously merely in fresh air may remain unconscious for some time and be ill for a day or two, while the other who is treated immediately with this inhalation goes back to work within a half hour or so and feels as well as before the gassing.

Physiological Response to Various Concentrations. When the time is measured in hours and the concentration of carbon monoxide in parts per million the physiological effect may be defined by the equations:

Time $\times$ concentration $=$ 300, no perceptible effect
Time $\times$ concentration $=$ 600, a just appreciable effect
Time $\times$ concentration $=$ 900, headache and nausea.
Time $\times$ concentration $=$ 1500, dangerous.

Similar data in a more conventional form are as follows:

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF CARBON MONOXIDE.[1]

	Parts of Carbon Monoxide per Million Parts of Air
Concentration allowable for an exposure of several hours..	100
Concentration which can be inhaled for 1 hour without appreciable effect	400 to 500
Concentration causing a just appreciable effect after 1 hour exposure	600 to 700
Concentration causing unpleasant but not dangerous symptoms after 1 hour of exposure.....	1000 to 1200
Dangerous concentration for exposure of 1 hour.....	1500 to 2000
Concentrations which are fatal in exposures of less than 1 hour	4000 and above

[1] Henderson, Haggard, Prince, Teague, and Wunderlich, J. Ind. Hygiene, 1921, III, pp. 79, 137.

Cyanogen Compounds. The following table presents the more important volatile cyanogen compounds with their general physical and physiological data so far as they are known.

VOLATILE CYANOGEN COMPOUNDS.

Name	Formula	Boiling Point, ° C.	Physiological Action
Cyanogen	C_2N_2	— 34.4	Arrest oxidation in the tissues and thus produce asphyxia.
Hydrocyanic acid	HCN	26.0	
Acetonitrile	CH_3CN	81.0	
Propionitrile	C_2HCN	97.0	
Methyl isonitrile	CH_3NC	58.0	
Ethyl isonitrile	C_2H_5NC	82.0	
Benzonitrile	C_6H_5CN	119.0	
Cyanogen chloride	CNCl	15.5	As above but also irritating to the respiratory tract.

Occurrence. Hydrocyanic acid gas and cyanogen are used as disinfecting agents in ridding ships or buildings of vermin. The acid is evolved when celluloid is burned and appears in small amounts in blast furnace gas and in impure coal gas. It is also evolved from its alkali salts by contact with air; these salts are used extensively in various industries such as the extraction of gold from its ore. The nitriles and cyanogen chloride are little used. The latter substance is distinguished from the rest of the cyanide compounds by its pronounced irritating action upon the respiratory tract.

Action of Cyanides. The cyanogen compounds are true protoplasmic poisons in the sense that they arrest the activity of all forms of living matter. They exert an inhibiting action upon tissue oxidation, presumably by combining with the catalysts in the living cells of the body tissues containing iron or sulfur. The tissues manifest life by heat and movement, and the continual oxidation of foodstuffs. Cyanides stop this oxidation, and the vital functions are suspended. The suspension is maintained only during the presence of the cyanide; its removal allows the return of normal function, if death has not occurred during the period of oxygen starvation. Cyanide poisoning is a form of asphyxia caused by the arrest of internal respiration.

Cyanide combines with hemoglobin in vitro with difficulty but readily with methemoglobin to form cyanomethemoglobin. The combination of cyanide with hemoglobin does not occur in the body except in the presence of methemoglobin, and hence as a postmortem change. The bright red color of the venous blood in cyanide poisoning is due to the fact that oxygen is not abstracted from the blood in the tissues, and the blood therefore returns in the veins still in the arterial condition.

The cyanides are rapidly destroyed in the body, combining with sulfur to form non-toxic sulfocyanides.

Symptoms of Cyanide Poisoning. Acute cyanide asphyxia is one of the most rapid modes of death, for the reason that the use of oxygen by the tissue is prevented, altho respiration continues for a brief period, and during this time is greatly increased in volume. In the ordinary case of acute poisoning, the man falls after a few breaths of the atmosphere contaminated with the gas. Death follows in 6 to 8 minutes.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF HYDROCYANIC ACID GAS.[4]

	Parts of Hydrogen Cyanide per Million Parts of Air
Slight symptoms after several hours exposure	20 to 40
Maximum amount that can be inhaled for 1 hour without serious disturbance	50 to 60
Dangerous in 30 minutes to 1 hour	120 to 150
Rapidly fatal	3,000

[4] Kobert, R., Kompend. der prak. Toxicol., Stuttgart, 1912.

In less acute but still fatal cases the sequence of events is less rapid and symptoms typical of asphyxia are more clearly seen. Mild cases and non-fatal cases of poisoning result in headache, a feeling of suffocation, and some nausea; these symptoms pass off after several hours.

The other cyanogen compounds are in varying degrees less toxic than hydrocyanic acid.

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Chapter VIII.

Group II. Irritant Gases, Their Action, Acute and Chronic, and Sequelae.

The irritants constitute a large group of the gases and vapors occurring in industry; they include such common substances as acid fumes, chlorine, ammonia, and sulfur dioxide. The substances designated as irritants differ widely in chemical and physical properties. They have, however, one property in common: they induce inflammation in tissues with which they come into direct contact. This effect seems to exhaust their power to injure, for they are not usually absorbed into the blood in any considerable amount; thus they cannot affect tissues reached only thru the blood. The effects of the irritant gases are manifested therefore almost solely in surface tissues, the skin, conjunctiva of the eyes, and particularly the membranes of the respiratory tract.

Similarity of Action but Dissimilarity of Symptoms.

Widely different symptoms result from the action of the various irritant gases. Fundamentally, however, the toxicology of all volatile irritants is the same. The differences in symptoms are essentially the results of differences in the localities elected by the irritants for their action. The characteristic symptomatology of any irritant is, therefore, an expression of the particular structure in which inflammation is induced rather than of any fundamental dissimilarity in the actions of the irritants. Some irritant gases act primarily upon the upper respiratory tract and induce pharyngitis and laryngitis. Others act chiefly upon the lungs, and cause pulmonary edema and pneumonia. The symptoms of laryngitis induced by an irritant gas are quite different from those of pneumonia, but so for example are the symptoms arising from a burn upon the palm of the hand and one on the eyeball. The burns in these two localities have a different symptomatology merely because of the difference in the structures affected.

Locus of Action.

Just as in the case of burns the locus influences the effect, so the differences in symptomatology and pathology which occur as the result

of poisoning by different types of irritant gases are chiefly dependent upon the locus of their action. For example, ammonia produces intense congestion of the upper respiratory passages and immediate death from spasm or edema of the larynx. On the other hand, phosgene and nitrogen peroxide cause little irritation of the upper respiratory tract, but induce pneumonia or pulmonary edema thru their action upon the alveoli of the lungs. Chlorine is intermediate in its action between ammonia on the one hand and phosgene and nitrogen peroxide on the other. Such distinctions in the actions of irritant gases are due to the differences in the locality in the respiratory tract upon which they act.

Characteristics of Gases and Point of Attack.

The election of certain localities for action by the various irritants is the result, not so much of the difference in their chemical properties, as of the differences in their physical properties. Once this distinction is clearly comprehended, a knowledge merely of the physical properties of an irritant gas is sufficient to indicate the part of the respiratory tract which it will affect and the symptomatology and pathology which will follow. It thus becomes possible to systematize the irritant gases and vapors and their actions.

The severity of the effects is greatest upon those surfaces which are most easily penetrated and particularly upon those which are moist. Therefore the epithelium and mucous membrane of the respiratory passages and the conjunctiva are the seats of primary election. A concentration of ammonia vapor which is intolerable to the eyes and throat may cause no appreciable irritation of the skin when it is dry. When the eyes and respiratory tract are protected with a gas mask high concentrations of ammonia can be tolerated, but to this also there is a limit at which the skin is attacked.

The selective action of the various irritants upon different parts of the respiratory tract is due primarily to the differences in the solubility of the gases. Thus a gas which is readily soluble in water is taken out of the inspired air by contact with the first moist tissue which it reaches. As a consequence the upper respiratory tract bears the brunt of the action; the lungs are relatively little affected, since the concentration of the irritant which reaches them is greatly reduced by absorption in the upper passages. In the case of those gases which have a low solubility in water, the upper respiratory passages suffer little, for little is absorbed, and the main damage is done deep in the lungs. A gas of moderate solubility exerts its action more or less uniformly thruout the entire respiratory tract. Thus the irritant gases are dangerous inversely as their solubility. The less soluble any one of them is the more insidious it is.

Solubility the Determining Factor.

A simple experiment illustrates how the solubility of the particular gas determines its selective action as between the various parts of the respiratory tract: Each of the various gases in turn is diluted with a large volume of air in a suitable vessel, and is then passed slowly thru a long glass tube containing a strip of filter paper moistened with water and extending the entire length of the tube. If the gas is alkaline or acid in character litmus paper may be substituted for the filter paper. The amount of each gas which is absorbed in the water held by the paper in different parts of the tube is chiefly determined by the solubility of the particular gas. The nearer end is saturated first. For a readily soluble gas the amount absorbed in that locality is large, the amount further on comparatively small, while the air which passes out at the effluent end of the tube is practically free from the gas. On the other hand, the amount of a slightly soluble gas absorbed during the passage thru the tube is small, and the concentration which passes out at the effluent end is high. In this experiment the tube thru which the gas passes is analogous to the respiratory passages: the nose, throat, trachea and bronchi. The effluent gas is that which would pass into the lungs.

In this artificial system the continued passage of the gas results in an increase in the concentration of the dissolved substance in the fluid, until further absorption of the gas from the air ceases; the effluent air then approaches the affluent concentration of gas. With a few exceptions, this does not occur in the living body. Equilibrium is not reached between the irritant gas in the air and the fluid of the tissues. Most irritants cannot exist as the free substance while in contact with the tissues, but are combined with or altered by them as an essential part of the initial irritation or injury which later results in inflammation.

Thus with some of the highly soluble irritant gases a considerable reduction in the concentration is effected by absorption in the fluids of the upper respiratory tract; and this is important because it leads to altogether disproportionate effects upon the lungs from high and low concentrations of the more soluble irritants. For this reason the severity of the action of an irritant gas does not vary in proportion to the product of the amount of the gas in the air multiplied by the duration of exposure to it, as we have seen to be the case with such an asphyxiant as carbon monoxide. A high concentration for even a short time has an intense effect. A reduction of one-half would allow it to be withstood for much more than twice as long, and with less effect. Consequently any reduction in the concentration of the irritant during

its passage thru the upper part of the respiratory tract results in a more than proportionate sparing of the tissues of the lungs.

Injury at Different Levels of Respiratory Tract.

The importance of the selective action of irritant gases in the respiratory tract bears directly upon the relative danger of death from injuries in the different localities. The delicacy of the respiratory membranes, their susceptibility to injury and the seriousness of the damage which results are very different in the upper and lower respiratory tract. The nose and pharynx may be stripped raw and yet suffer little permanent damage. It is a more serious matter when the larynx and bronchi are injured. The local effects are very painful or even dangerous, and general systemic effects also develop just as in the case of acute laryngitis or bronchitis from bacterial infection. But the most serious results of inhalation of an irritant gas occur when the lungs are directly acted upon. The damage then gives rise to acute response in edema leading to suffocation or, if this danger is escaped, to pneumonia with prostration and failing circulation. The outcome of either process may be fatal.

Inflammation not Corrosion.

It must be clearly understood that inflammation even of the most intense character, with destruction and sloughing of the tissues, is a process totally distinct from simple chemical corrosion. The phenomena of inflammation are induced by the alteration of the normal vital process in the tissues with which the irritant is brought in contact. The initial step is coagulation, liquefaction, dehydration or some other disturbance of the normal state of the protoplasm caused by the vapor. The type of the initial change induced by the irritant depends upon the chemical nature of the substance. But the inflammation which follows is independent of the nature of the initial insult and is essentially the same for all irritant gases.

The initial reaction of irritants with the tissues with which they are brought in contact is chemical or physical and can be initiated *in vitro* by the action of the irritants upon protein. But *in vivo* these effects are usually not sufficiently intense to be visible. What we see and what the patient feels as the result of the action of the irritant is the vital reaction which is made by the tissues in response to the irritation. The consequent inflammation is a physiological reaction and not merely a direct chemical effect. When hydrochloric acid acts upon zinc the metal is dissolved with the evolution of hydrogen gas. When hydrochloric acid acts upon living tissue, the comparable direct effect is usually slight and almost or entirely invisible. Soon, however, the

disturbed vital process of the affected tissues manifests itself physiologically. If the tissues were already dead, as in a corpse, high concentrations of the chemical, even far above the toxic minimum, would induce no visible effect. In other words, the effect of irritant gases, except in cases of the most exceptional intensity, is not simple and direct corrosion. The irritant gases act in such extreme dilution that such gross effects are not usually at all involved. When chemical corrosion does occur to any considerable extent, the shock may cause almost instant death.

Inflammation of the Upper Respiratory Tract and Bronchi.

Inflammation is then a reaction of living tissue in response to irritation. The first visible reaction is redness due to the dilatation of the small vessels adjoining the area acted upon by the irritant. In mucous membranes this initial step is accompanied by increased activity of the mucous glands; a profuse flow of mucus is secreted over the irritated surface. In moderate exposure to gases which affect the upper respiratory passages the inflammation may not extend beyond this stage; and the symptoms are then merely those of general mild pharyngitis and laryngitis. Recovery takes place by the return of the vessels to their normal state without leaving any lesion.

If the irritation is severe, the inflammation does not stop with rubefaction and increased flow of mucus. Plasma exudes from the walls of the engorged vessels, thus producing swelling, separation of the tissues and their consequent death, or it exudes into the respiratory passages and spaces and blocks them. In the upper respiratory passages and bronchi these changes appear first as a loss of normal gloss and translucency together with some swelling. The plasma which exudes clots upon the surface and is frequently streaked with extravasated blood. The tenacious layer thus formed may appear as a false membrane. In severe cases the mucosa may be stripped from the submucosa and lifted by the fluid. The tissue sloughs off leaving raw and oozing surfaces covered with mucopurulent material.

The symptoms of severe membranous bronchitis and tracheitis accompany these inflammatory changes and may persist for several days. In the nonfatal cases the mucous membrane then begins to regenerate outward from the edges of patches of relatively uninjured epithelium where folds in the mucosa have protected it. In the large bronchi the repair is usually effected with little permanent scarring; the smaller bronchial tubes may, however, show some permanent thickening. Before the regeneration of the mucosa can occur, however, infection of the bronchi almost always develops, since the normal barrier to bacterial invasion is removed.

In severe cases of inflammation of the upper respiratory tract the larynx may become so swollen from the extravasation of fluid into the tissue that the opening into the trachea is occluded, and death then occurs from acute suffocation. Laryngeal edema is the common cause of rapid fatality during or soon after severe exposure to those irritant gases which act on the upper respiratory tract.

Inflammation of the Lungs.

The outstanding feature of inflammation in the lungs resulting from the action of irritant gases is pulmonary edema. The condition reaches its height in from 12 to 24 hours after the exposure. If death does not occur, it tends to regress within 48 hours.

The edema results from inflammatory changes similar to those which occur in the upper respiratory passages. The epithelium of the finer air sacs in the lungs, both of the atria and alveoli, is damaged by the irritant. Fluid extravasates from the capillaries and accumulates between the cells. Fluid also escapes into the alveolar spaces, coagulates and fills them with fibrin, thus seriously interfering with the respiratory exchange of oxygen and carbon dioxide between the air and the blood. At the same time the flow of blood thru the lungs is obstructed and a severe strain is thus placed upon the right side of the heart. The loss of fluid from the blood in the form of exudate may be of a quantity sufficient seriously to deplete the body of water and to result in an increase in the viscosity of the blood.

The edema induced by irritant gases differs from the edema of nonirritant origin in that the latter is usually particularly marked in the pendant portion of the lungs, while the edema arising from irritation is not greatly affected by gravity or the posture of the subject. Not all parts of the lungs, however, are equally involved in the inflammatory changes arising from the action of irritant gases. The irritant action upon the smaller bronchial tubes may cause some of them to constrict, so that the portions of the lungs to which they lead escape the action of the gas. Owing to this bronchoconstriction as well as to the plugging of the bronchi with sloughed mucosa and fibrin, areas of atelectasis and emphysema may occur in the edematous lung.

Irritation of the lungs does not give rise to severe pain as does inflammation of the upper passage. The principal symptoms are those of asphyxia. This asphyxia, however, is of a peculiar character since its early stages are not associated with marked air hunger. The patient may present only an ashy gray color, no dyspnea, and yet the slightest exertion may cause immediate death. The state of gray cyanosis without marked dyspnea is due to anoxemia unattended by increased carbon dioxide in the blood. In a later stage purple cyanosis and intense

air hunger characterize the clinical picture. In this condition the edema is so severe that it interferes with the elimination of carbon dioxide as well as the absorption of oxygen; accordingly the classical symptoms of suffocation develop.

The peculiar features of early pulmonary edema, the stage of gray cyanosis, are due to the unequal ventilation of the blood with respect to carbon dioxide and oxygen. Carbon dioxide is much more soluble than oxygen in the plasma which covers the surface of the alveoli. Oxygen diffuses thru the pulmonary membrane less readily than carbon dioxide, and its absorption is much more readily affected than is the elimination of carbon dioxide. In this respect the anoxemia of early pulmonary edema is similar to that of mountain sickness. At first, therefore, the exchange of oxygen is hindered to a greater degree than is that of carbon dioxide, and the oxygen of the blood is decreased without any appreciable rise of carbon dioxide. There may even be a decrease of carbon dioxide owing to some degree of overbreathing, for oxygen deficiency is a stimulant to respiration, altho a relatively weak one. Thus the signs of asphyxia at this stage are not very striking, altho the condition is acutely dangerous.

With the progress of the edematous condition, some of the alveoli become filled with frothy fluid, and the terminal bronchioles become plugged. Such areas then take little part in the gas exchange of the lungs, and the air occluded within then comes to have the same gas pressures as the venous blood. At the same time areas which are less involved in the edema are hyperaërated, and the carbon dioxide in the blood passing thru them is reduced below the normal level. Hyperaëration cannot, however, raise the oxygen content of the blood passing thru these parts of the lungs above the amount which the hemoglobin normally holds. The characteristics of the oxyhemoglobin dissociation curve permit no more. Under these conditions the blood which reaches the left side of the heart is a mixture; one portion has the same content of gases as the venous blood, while the other approaches the normal arterial blood in its content of oxygen, but is lower than normal in carbon dioxide. The mixture of over- and under-aërated blood which is pumped into the arteries is thus low in oxygen; but, during the early stages, it is not far from normal or even below normal in respect to carbon dioxide.

As the edema progresses the diffusion of carbon dioxide as well as that of oxygen is interfered with to an increasing extent. The pressure of carbon dioxide in the arterial blood rises, probably the blood alkali also decreases, while anoxemia becomes more and more intense, and all three conditions contribute to the intense air hunger. The more marked symptoms depend upon the excessive pressure of

carbon dioxide in the arterial blood, but the more serious damage results from the deficiency of oxygen. The asphyxia of lung edema arising from irritant gases, therefore, is more dangerous than the superficial signs indicate. Consequently it frequently happens that a man who appears to be only slightly affected is allowed, or told, to make some movement, such as sitting up in bed so that a physician may listen to the râles in his lungs; and as the result of this slight exertion he falls back dead. This is probably the failure of an overworked and asphyxiated heart.

Treatment of Pulmonary Edema.

Severe edema of the lungs usually terminates fatally. In nonfatal cases the acute symptoms of the gassing usually diminish within forty-eight, or at most seventy-two hours, and are followed by symptoms of bacterial infection. Medicinal measures contribute little to the relief of pulmonary edema, altho in some cases benefit may be derived from the intravenous administration of saline solution; and this infusion may be combined with the withdrawal of blood, when the venous congestion is intense. Inhalation of oxygen tends to relieve the anoxemia and cyanosis and should always be begun as early as possible in the stage of gray cyanosis. As in the case of pneumonia it is important to begin the inhalation while the symptoms are slight, instead of waiting, as is usually done, until the patient has suffered loss of strength and functional impairment from anoxemia. It is not sufficient merely to discharge oxygen from a funnel held over the face, for only a negligible amount is then inhaled. For the inhalation to be effective, an efficient inhalator and a close and comfortably fitted mask must be used. With such an inhalator it is best not to administer pure oxygen, but a mixture of oxygen and air just sufficiently rich to counteract the cyanosis. By far the most important feature of treatment in such cases is absolute quiet and rest. Neglect of this requirement is common and frequently precipitates death by sudden heart failure.

Infection as a Sequel to Inflammation.

The inflammation of the respiratory tract induced by the irritant gases lessens or removes the normal barrier to bacterial invasion. Consequently infection is a common sequel to the action of this class of gases. The organisms involved in this infection are usually those which normally inhabit the upper respiratory tract. The symptoms are identical with those of infections of nonirritant initiation.

Even an exposure to irritant gases insufficient to induce the acute symptoms of lung irritation may lead to the development of pneumonia.

Under industrial conditions the infections thus induced constitute a greater cause of death than does primary pulmonary edema. It is probable that inhaling irritant gases or vapors even in extreme dilution predisposes to the development of infection of the respiratory tract. Sulphur dioxide in the coal smoke of cities and irritant vapors from the exhaust of automobiles on city streets probably contribute to the frequency of the respiratory infections in urban districts. The comparative mortality from bronchopneumonia among workers in chemical factories in England is reported as twice that for all males, and more than eight times as great as for farmers.

Tuberculosis as a Sequel to Inflammation.

On the other hand, there is considerable uncertainty as to the rôle of irritant gases as a predisposing factor in the development of pulmonary tuberculosis. The disease cannot be said to arise as a direct sequel of irritation of the lungs as is the case with pneumonia. The statistics of the subsequent health of soldiers gassed during the war indicate that, when the lungs have once healed, they are not appreciably more liable to tuberculosis than would otherwise have been the case. Nevertheless, when the subject has suffered a period of decreased vitality or ill-health as the consequence of the action of irritant gases upon the respiratory tract, or as a result of the subsequent infection, then tuberculosis may develop as a recurrence of a previously existing lesion, just as is often the case following decreased vitality from any other cause. It often happens that the subject was not aware of this preëxistent but dormant infection; indeed, it may not have been found even by physical examination. In considering tuberculosis, it is necessary to assume that every healthy person carries a dormant infection and that the disease is liable to become clinically evident whenever the resistance of the body is lowered sufficiently. Thus gassing may fairly be said to be, in the ordinary use of the word, the cause of a tuberculosis progressing steadily from the occurrence of poisoning. But it cannot properly be regarded as the cause of a tuberculosis developing at some time subsequent to virtually complete recovery from the gassing itself. The crux of the question in any particular case is whether or not the gassing has undermined the patient's general health to an extent sufficient to allow the development of tuberculosis.

Chronic Effects of Exposure to Irritant Gases.

Long continued derangement of health may arise in two distinct ways from exposure to irritant gases: (1) As a chronic inflammation following a single severe exposure to the gas, and (2) as a chronic

inflammation caused and maintained by continued exposure to low concentrations of the irritant.

After a severe irritation of the lower respiratory tract and subsequent bacterial invasion, this infection sometimes persists as a chronic condition and produces a protracted period of ill-health. The most characteristic features are chronic bronchitis, cicatrization of the lungs and obliteration of a portion of their deeper structure, sometimes with abscess formation. In some of these cases, physical examination may give little evidence of persistent pulmonary change. The subject at rest appears normal, but he is incapable of any, except the most moderate, exertion. This condition may persist for a long time. In view of the fact that direct pharyngeal inspection and x-ray examination fail to reveal conditions to explain the disablement, malingering may be suspected; but unjustly.

The bacterial infection following inflammation may, in the process of healing, leave focal infections and necrotic areas pocketed in the lung or bronchiolar tissues. Such persistent infections are the cause of long continued ill-health with symptoms similar to those which arise from focal infection of any other origin.

The second type of chronic inflammation arises from prolonged exposure to sublethal concentrations of irritant gases. The distinguishing feature of the poisoning is a catarrhal inflammation of the upper respiratory tract. If the exposure is more or less a regular part of the man's working conditions, the sharp cough present in the beginning of the inflammation becomes less marked. The worker then appears to have acquired a partial tolerance to the gas. No true tolerance exists, however, toward any irritant gas. The appearance of tolerance arises from the fact that the protective reflexes, especially coughing, are less active because the surface of the upper respiratory tract is covered with tenacious mucus, and thus is partially shielded from the action of the gas. The catarrhal exudate does not, however, afford any protection to the deeper respiratory structures. It rather exposes them the more to the action of the gas, because of the partial abolition of the respiratory reflexes. In addition the inflammation diminishes the normal protection against bacterial invasion. The condition is therefore detrimental to the general health and greatly increases the susceptibility to acute infections of the respiratory tract.

Protective Reflexes.

The so-called protective reflexes do not in reality actually protect the respiratory tract from the action of irritant gases. They, nevertheless, play an important rôle in furnishing a warning of the presence of irritants in the inspired air, particularly those irritants which attack

the upper respiratory tract. One of the features which renders especially dangerous any exposure to those gases which primarily attack the lungs is the fact that they do not greatly irritate the upper respiratory tract; phosgene and nitrogen peroxide are especially notable in this respect. Lethal concentrations of these gases can be inhaled with less warning from irritation of the throat and from coughing than would be elicited by a concentration of ammonia, for example, well below an immediately dangerous level.

The protective respiratory reflexes consist in coughing, constriction of the larynx and bronchi, closure of the glottis, and inhibition of respiration. Coughing is initiated by even slight irritation of the larynx and consists of a series of expiratory blasts which tend to expel the stimulating material. Coughing obviously does not prevent the passage of irritant gases, but it warns of the presence of these substances. When higher concentrations of irritants act upon the larynx, the superior laryngeal nerve is stimulated, and respiration is inhibited with the chest in the position of expiration. The breathing is almost equally disturbed by stimulation of the sensory fibers of the trigeminal nerve in the nasal passages; this causes sneezing. With severe irritation, the glottis is closed reflexly by constriction of the adductor muscles, and the bronchial musculature is constricted, so that the passages to the lungs are partially closed. The inhibition of respiration is usually only temporary and is broken thru by the increasing excitement of the respiratory center, owing to the lack of ventilation and the increasing venosity of the blood. Occasionally the spasm of the glottis may persist so long that symptoms of acute asphyxia are induced. The constriction of the bronchi, particularly of the smaller tubes, may be sufficient to prevent the entrance of the gas into some portions of the lungs even under the most acute conditions, and areas of atelectasis and emphysema may result.

Absorption of Irritant Gases or Their Products.

The action of most of the irritant gases upon the respiratory tract results in their destruction or neutralization, and for this reason they are not absorbed into the body in their original form. The products of this destruction or neutralization do not as a rule cause any systemic poisoning after absorption. There are, however, a few exceptions to this rule, notably hydrogen sulfide and nitrogen peroxide. When hydrogen sulfide is absorbed in the respiratory tract it is neutralized to sodium sulfide. The process causes intense local irritation, but in addition profound systemic poisoning is produced by the absorption of this alkaline sulfide into the blood stream. In the same way sodium nitrite is formed as a result of the inhalation of nitrogen

peroxide, and may induce symptoms of nitrite poisoning; with this gas, however, these general effects are usually concealed by the much more acute pulmonary irritation.

A few substances, which are generally considered as more or less irritating, but which are not here classed as irritants, are absorbed unchanged from the respiratory tract. These are chiefly organic substances such as alcohols, ethers, aldehydes, the volatile constituents of petroleum and of coal tar, etc. They are not altered or destroyed by contact with living tissue. Their systemic effects are as a rule greater than their action as pulmonary irritants.

The local action of these substances differs from that of the gases which are primary irritants in two respects: (1) The mucous secretion which results from their action upon the respiratory passages does not serve to form a protective coating against their action; for the secretion neither neutralizes nor alters these substances, but rapidly becomes saturated with the gas at the tension inhaled. (2) The greater part of the irritant action occurs in the upper respiratory passages, bronchi and bronchioles, while the lung alveoli and atria are relatively little affected. Such amounts of the gas as reach the lungs themselves are absorbed and are the cause of systemic, but not of pulmonary, symptoms. In this respect these substances are exceptions to the rule that the less soluble the irritant gas the less it affects the upper, and the more it injures the lower respiratory tract; for the solubility of these substances is usually quite low. The sparing of the deeper portion of the lungs is due to the active absorption into the blood which prevents accumulation of the irritant in the alveoli.

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As the irritant gases have been used preëminently in war, most recent reviews in this field deal with the topic from that standpoint.

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Chapter IX.

Group II (continued). Special Characteristics of Various Irritant Gases.

The principles formulated in the preceding chapter afford a general explanation of the physiological action of all irritant gases. The need for extensive, complicated and special description for each particular gas is thus obviated. The present chapter is limited therefore to a classification of the irritant gases, largely on the basis of their solubility, to discussion of some exceptional characteristics of particular gases, and to a series of brief descriptions of the conditions under which the various gases of this class occur.

Classification of Irritant Gases.

Irritant gases are conveniently classified into four subgroups according to the site of their action in the respiratory tract and consequent symptomatology.

Subgroup I includes those gases which act primarily upon the upper respiratory tract.

Subgroup II, those gases which act upon the upper respiratory tract but also spread their action to deeper structures.

Subgroup III, those gases which act primarily upon the lungs and only to a much less extent upon the upper respiratory tract.

Subgroup IV, those gases which are not altered or destroyed by contact with the tissues of the respiratory tract, and do not strictly follow the generalization set forth in the preceding chapter.

Subgroup I.

Ammonia Gas.

At ordinary temperatures ammonia is a colorless gas with a specific gravity of 0.597. It is one of the products of the putrefaction of nitrogenous substances. Near putrefying substances the amount of ammonia may be of the order of 0.01 to 1.0 mg. per liter of air. Except in the immediate neighborhood of the decomposing material, however, ammonia does not exist in the air in the free state, but is combined usually as the carbonate.

Ammonia results from the destructive distillation of bones, and also from that of coal in the manufacture of coal gas; the latter is the ordinary commercial source. Ammonia is usually supplied and shipped either in liquefied form in steel cylinders or dissolved in water as the hydrate. The aqueous solution yields the gas on exposure to air.

Liquid ammonia is extensively employed as a refrigerant in cold storage plants and for the manufacture of artificial ice. If a pipe or joint breaks or leaks, ammonia gas escapes into the air and quickly becomes intolerable for everyone in the vicinity who is not wearing a gas mask. Contamination of the air occurs also from the bursting of cylinders of the liquid during filling, storage or transit. The aqueous solution of ammonia has a wide application in the arts. Serious accidents rarely occur from its use except thru the accidental spilling of ammonia water in the attempt to revive unconscious persons by the inhalation of the substance. Such accidents are best avoided by not using ammonia for this purpose, particularly as it is probably of no real value.

The alterations in respiration and the action of the heart as the result of inhaling ammonia are produced reflexly from the irritation of the upper respiratory tract. This reaction consists in a general vasoconstriction and considerable increase of breathing; if the concentration is high respiration is stopped. The effects of inhaled ammonia are entirely upon surface tissues; none is absorbed.

Physiological Response to Various Concentrations of Ammonia.

	Parts of Ammonia per Million Parts of Air
Least detectable odor[1]	53
Least amount causing immediate irritation to the eye[1]	698
Least amount causing immediate irritation to the throat[1]	408
Least amount causing coughing[1]	1,720
Maximum concentration allowable for prolonged exposure[2 and 3]	100
Maximum concentration allowable for short exposure (½ to 1 hour)[2 and 3]	300 to 500
Dangerous for even short exposure (½ hour)[3]	2,500 to 4,500
Rapidly fatal for short exposure	5,000–10,000

[1] U. S. Dept. of Interior, Bureau of Mines, Technical Paper 248, 1921, table facing page 66.
[2] Ronzani, E., Arch. f. Hyg., 1909, 70, p. 217.
[3] Lehmann, K., Arch. f. Hyg., 1886, 5, p. 1.

Hydrochloric Acid Gas.

Hydrochloric acid is a colorless gas with a specific gravity of 1.278. On exposure to air this gas forms dense white fumes from the con-

densation of atmospheric moisture and the formation of hydrochloric acid solution in minute drops like steam. The gas is rarely encountered in the anhydrous state and poisoning by this substance is therefore due to its aqueous solution. Hydrochloric acid gas is extremely soluble in water and is encountered commercially in solutions of various strengths. The more concentrated solutions give off some of the gas at ordinary temperatures which appear as white fumes in moist air.

Hydrochloric acid is prepared largely by the action of sulfuric acid upon sodium chloride as a by-product in the manufacture of soda ash. The solution of the acid is used extensively in the industries but usually in small amounts at any one time, except during the manufacture of the acid and in the "pickling" of iron. In the latter process the iron to be cleaned is immersed in the acid. A copious evolution of hydrogen results, and each bubble escaping is coated with a film of acid which is carried into the air. The fumes from hydrochloric acid are occasionally encountered in large quantities by firemen in burning buildings, either storage depots or chemical factories containing supplies of the bottled acid.

In most cases the toxicity of hydrochloric acid is not that of the anhydrous gas but of the vapor which is produced by its combination with the moisture of the air. The toxicity of the gas is thus somewhat reduced before it is inhaled; for the anhydrous gas is without doubt more toxic than the moist acid. The occasional occurrence of unusually dry hydrochloric acid gas under some conditions of atmospheric heat and absence of moisture explains the increased degree of toxicity which this gas sometimes exhibits.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF HYDROCHLORIC ACID GAS.

	Parts of Hydrogen Chloride per Million Parts of Air
Maximum concentration allowable for prolonged exposure[3a]	10
Maximum concentration allowable for short exposure (½ to 1 hour)[3a]	50
Dangerous for even short exposure[3a, 4 and 5]	1000 to 2000

[3a] Lehmann, K., Arch. f. Hyg., 1886, 5, p. 1.
[4] Kohn-Abrest, Annales des Falsifications, 1915, **8**, p. 215.
[5] Leymann, Concordia, 1906, **13**, p. 120.

Sulfuric Acid.

Sulfuric acid is a liquid at ordinary temperatures, and as its boiling point is 338°C. it does not give off an appreciable amount of fumes. The so-called fuming sulfuric acid contains 30 to 50 per cent of dissolved sulfuric anhydride, and the fumes which arise from exposure

to air are due to this substance. When the ordinary concentrated sulfuric acid is heated, it gives off dense and irritating fumes. When the dilute acid is heated, very little sulfuric acid vapor is evolved until after the water has been expelled.

When hydrogen is evolved from a sulfuric acid solution the bubbles of gas carry into the air a finely divided spray of the acid. The air may become contaminated with this thin mist of sulfuric acid during the charging of lead storage cells or in the "pickling" of metals with sulfuric acid.

The toxic concentration for inhaled sulfuric acid is not recorded in the literature. Altho sulfuric is a more corrosive acid than hydrochloric, there is probably little difference in the toxic concentration as expressed in parts per million of air. The concentration as expressed in milligrams per liter of air are not, however, comparable because of the greater molecular weight of sulfuric acid.

Hydrofluoric Acid Gas.

Hydrofluoric acid gas is colorless, but forms a mist in moist air. At 19°C. it condenses to a colorless liquid. The anhydrous acid diluted with water to a specific gravity of 1.15 distills unchanged at 120°C. and is handled in this form commercially.

The acid is used to etch and polish glass. The production of artificial fertilizers from basic phosphates containing fluorides by treatment with sulfuric acid may involve the evolution of hydrofluoric acid and consequent poisoning.

Physiologically hydrofluoric acid is a much more active substance than is hydrochloric acid. Aside from the irritation induced by its acid properties, both hydrofluoric acid and its neutralization products, such as sodium fluoride, are direct protoplasmic poisons. Its inhalation results in the formation of deep ulcers in the upper respiratory tract. These ulcers are difficult to heal. Hydrofluoric acid is intensely caustic to the skin and conjunctiva. It causes many troublesome but usually slight accidents wherever it is employed, or it occurs, even in small amounts.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF HYDROFLUORIC ACID GAS.

	Parts of Hydrogen Fluoride per Million Parts of Air
Maximum concentration allowable for prolonged exposure[2]	3
Maximum concentration allowable for short exposure (½ to 1 hour)[2]	10
Dangerous for even short exposure[2]	50 to 250

[2] Ronzani, E., Arch. f. Hyg., 1909, 70, p. 217.

Formaldehyde.

Formaldehyde is a colorless gas. At temperatures of 20°C. and above, it polymerizes to paraform or trioxymethylene, $(HCHO)_3$. This polymerization is retarded by water, and for this reason formaldehyde is used commercially as the solution of the gas in water. The name formalin is applied to a solution of a strength of 37 per cent.

Formaldehyde is used in the manufacture of bakelite, in the preparation of dyes, as a preservative and extensively as a disinfectant. In the last use formaldehyde is employed both in solution and in the gaseous state.

The powerful irritant action of formaldehyde upon mucous membranes is due to its forming an irreversible combination with the protein of the surface cells. In contact with tissues formaldehyde is changed into formic acid and methyl alcohol thru the reaction:

$$2HCHO + H_2O = CH_3OH + HCOOH$$

Formic acid is an irritating acid but the neutralization product, sodium formate, is not particularly toxic. Methyl alcohol, however, and probably other methyl compounds formed by the breaking down of formaldehyde have a marked toxic action when absorbed. Systemic poisoning is said to follow the inhalation of formaldehyde and to exhibit a cumulative action analogous to that of methyl alcohol.[6] A number of fatalities have been recorded from the swallowing of solutions of formalin. In each of these cases the amount taken was more than .09 liter, 33 grams of formaldehyde. Recovery has been observed after a dose of .06 liter of formalin, or 22 grams of formaldehyde. From these amounts it appears that the systemic action of formaldehyde is not very intense. The serious symptoms following inhalation are induced by the local irritation; the amount absorbed from the respiratory tract plays a negligible part in acute poisoning. It is uncertain whether or not a systemic effect is produced by prolonged inhalation of low concentrations of formaldehyde. Brunnthaler believes that the decomposition products have a cumulative action. But in both acute and chronic poisoning from inhalation of the gas the outstanding feature is inflammation of the respiratory passages.

The toxic concentration of formaldehyde has not been determined quantitatively. Lewin[7] found it less toxic than acrolein.

Formaldehyde has an irritating action upon the skin; but different individuals show a marked difference in susceptibility to the irritation. After one severe inflammation a skin, which has previously been resistant, may become acutely sensitive to formaldehyde. Brunnthaler

[6] Brunnthaler, Zentralbl. f. Gewerbehygiene, 1914, II, 24.
[7] Lewin, L., Arch. f. exper. Path. u. Pharmakol., 1912, XLIX, 114.

believes that similar differences in susceptibility also occur, or may develop, to inhalation of the gas.

Subgroup II.

Sulfur Dioxide.

Sulfur dioxide is a colorless gas with a specific gravity of 2.23. It arises from the combustion of sulfur. It occurs in the gases issuing from volcanoes and is constantly discharged into the air of cities by the burning of coal containing sulfur. In the presence of moisture the dioxide may be oxidized and form sulfuric acid. Consequently no considerable quantities of sulfur dioxide are found in the outdoor air except in incompletely diffused smoke.

Sulfur dioxide under pressure in the liquefied state is used as a refrigerant in ice machines, usually on a small scale. It is also used as a fumigant and bleach. The gas is made in large quantities as a step in the manufacture of sulfuric acid and occurs in the gases arising from the smelting of ores containing pyrites. It is the main irritant (but not for men and animals the chief toxic substance, which is carbon monoxide) among the gases produced by the burning of coal. It is the constituent of coal smoke which is particularly injurious to vegetation. One part in a million in air contaminated with the smoke from railway engines may kill trees. Conifers are particularly susceptible.

Physiological Response to Various Concentrations of Sulfur Dioxide.

	Parts of Sulfur Dioxide per Million Parts of Air
Least detectable odor [8 and 9]	3 to 5
Least amount causing immediate irritation to the eyes [9]	20
Least amount causing immediate irritation to the throat [9]	8 to 12
Least amount causing coughing [9]	20
Maximum concentration allowable for prolonged exposure [9]	10
Maximum concentration allowable for short exposure (½ to 1 hour) [9 and 10]	50 to 100
Dangerous for even short exposure [10]	400 to 500

[8] U. S. Dept. of Interior, Bureau of Mines, Bulletin 98, 1915.
[9] Fieldner, A. and Katz, S., Eng. and Mining Jour., 1919, **107**, p. 693.
[10] Lehmann, Arch. f. Hyg., **18**, 180.

Acute poisoning from inhaling sulfur dioxide is rare for it is so irritating to the eyes and throat that lethal concentrations are almost irrespirable. In contact with the moist surface of the respiratory tract and conjunctiva sulfur dioxide is converted to sulfuric acid. The

action of sulfur dioxide is limited to the irritation of surface tissues for the sulfates arising as its neutralization product are not toxic.

Altho the action of sulfur dioxide is mainly in the upper respiratory tract severe exposure causes inflammation of the bronchi and occasionally edema of the lungs.

Chlorine.

Chlorine is a greenish yellow gas with a specific gravity of 2.47 as compared with air as 1. It is readily liquefied (its boiling point is —33.5°C.); and it is handled commercially in the form of liquid in steel cylinders or special tank cars. Chlorine is obtained during the electrolysis of sodium chloride for the manufacture of sodium hydroxide.

Liquid chlorine is used extensively to disinfect the water and sewage of cities; for recovering tin from scrap plate; for bleaching cotton, paper, and flour; and for the manufacture of disinfecting agents, such as chloride of lime and other chemicals. Extensive contamination of the air with chlorine occurs occasionally during fires in buildings where the cylinders are stored. The cylinders are tested to 3000 pounds pressure, but are equipped with safety plugs which release the gas slowly before the pressure has reached this point and thus prevent the bursting of the cylinders. The pressure developed in the cylinders during fires leads to the escape and rapid volatilization of the chlorine.

It is commonly supposed that chlorine reacts with the moisture on the tissues to form hydrochloric acid, and that its detrimental effects arise from the action of this acid. The similarity between the action of chlorine and hydrochloric acid is pointed out in support of this view. The similarity, however, is more apparent than real. Chlorine is nearly 20 times as toxic as hydrochloric acid and, because of its relatively low solubility, its locus of action in the respiratory tract is much more extensive than is that of hydrochloric acid. A more probable theory of the action of chlorine is that it affects moist tissues in the same way that it does other moist organic material, namely, by the abstraction of hydrogen from the water present, the liberation of nascent oxygen, and then the formation of hydrochloric acid. Oxidation is thus the major factor which, together with the action of the acid, induces irritation of the tissues.

In plants where chlorine is used there is a general belief that traces of the gas in the air exert a prophylactic action against diseases of the respiratory tract, possibly by keeping the bacterial content in the air at a low level. Altho this impression has not generally been confirmed experimentally, nevertheless the inhalation of low concentra-

tions of chlorine has been widely advocated as a treatment for head colds. The benefit derived is doubtful; the ill effects in some cases are certain.

High concentrations of chlorine have an irritating action upon the skin, but such irritation only occurs when exposure to the high concentrations is rendered tolerable by the use of a gas mask. Chlorine rash, an irritative dermatitis, has been reported as prevalent in German works where chlorine is made by electrolysis. This dermatitis does not result directly from the chlorine, but is produced by a chlorinated tar product arising from the action of the gas upon the tar cement at the anode of the cell.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF CHLORINE.

	Parts of Chlorine per Million Parts of Air
Least detectable odor[1]	3.5
Least amount causing immediate irritation to the throat[1]	15.1
Least amount causing coughing[1]	30.2
Maximum concentration allowable for prolonged exposure[1]	1.0
Maximum concentration allowable for short exposure (½ to 1 hour)[11]	4.0
Dangerous for even short exposure[11]	40 to 60
Rapidly fatal for short exposure[11]	1,000

[1] U. S. Department of the Interior, Bureau of Mines, Technical Paper 248, 1921.

[11] Kobert, R., Kompendium der prak. Toxikol, Stuttgart, 1912.

Bromine.

Bromine is a reddish brown liquid which boils at 58.7°C. When exposed to the air a heavy reddish vapor is evolved. In chemical properties bromine resembles chlorine to such an extent that little use has been made of it except in the manufacture of special chemicals, for the more abundant chlorine fulfills the purposes to which bromine might otherwise be applied.

The toxic action of bromine is essentially like that of chlorine, but it is somewhat less irritating to the lungs than is chlorine. The physiological response to various concentrations is roughly the same as in the case of chlorine.[11]

Iodine.

Iodine is a solid which volatilizes slightly at ordinary temperatures. As the temperature is increased purple fumes are evolved. The action

[11] Kobert, R., loc. cit.

of iodine is similar to chlorine and bromine, but it is more irritating to the lungs.

Acrolein.

Pure acrolein is a colorless liquid which boils at 52°C. On exposure to air acrolein is slowly oxidized to acrylic acid. This acid has not the irritating properties characteristic of acrolein.

Acrolein or acrylic aldehyde is formed as heavy fumes when oil or grease is burned. It is a troublesome by-product arising from the rendering of fats in making soap, in the boiling of linseed oil, and in melting down printers' type covered with oily ink. It is the main irritant in the exhaust gas from internal combustion engines; it comes from the burning of the oil used to lubricate the cylinders.

Altho acrolein primarily affects the upper respiratory tract in the relatively low concentrations ordinarily inhaled, it is nevertheless said [12] to induce edema of the lungs when inhaled in high concentrations by animals. Prolonged exposure to low concentrations of acrolein causes catarrhal inflammation in both the pharynx and larynx. The toxic concentrations of acrolein are the same as those of phosgene.[13]

Hydrogen Sulfide.

Hydrogen sulfide is both an irritant and a general poison. The latter aspects of its action will be dealt with in Chapter XIV. It resembles chlorine in its action upon surface tissues of the respiratory tract but is much less irritating. Immediate death from hydrogen sulfide is due to its systemic action; for this gas has an immediate lethal toxicity not far below hydrocyanic acid. The occasional delayed death, one to four days after exposure, is the result of its irritant action upon the lungs. Pulmonary irritation of a lesser degree also occurs as the result of prolonged exposure to low concentrations, below 50 parts per million of air.

Hydrogen sulfide even in low concentrations exerts a marked irritation upon the cornea of the eye. The surface epithelium is eroded, presumably by the sodium sulfide formed from hydrogen sulfide. There is usually marked photophobia. The eyes feel as tho grains of sand were on their surface. The action of the gas upon the eyes is limited to irritation of the surface and does not arise, as is sometimes supposed, from the absorption of the gas from the respiratory tract.

[12] Iwanoff, Arch. f. Hyg., 1917, LXXIII, 307.
[13] Chemical Warfare Service, Monograph XV, Washington, 1918.

Subgroup III.

Nitrogen Dioxide, "Nitrous Fumes."

There are three common oxides of nitrogen: nitrous oxide N_2O, nitric oxide NO, and two forms of the dioxide, NO_2 and N_2O_4.

Nitrous oxide has no irritating action and is used extensively as an anesthetic for surgical operations. Its anesthetic action is rather weak and appears only when the gas is inhaled in high concentrations. For prolonged anesthesia it must be mixed with oxygen. When inhaled without oxygen nitrous oxide is properly classified among the simple asphyxiants.

Nitric oxide does not exist in atmospheric air, for in the presence of moisture and oxygen it is converted into the dioxide.

Nitrogen dioxide in the form of N_2O_4 is a colorless liquid which has a boiling point of 26°C. Nitrogen dioxide in the form of NO_2 is a gas almost black in color. The molecular form of the oxide is determined by the temperature. Thus on heating, the colorless N_2O_4 is first changed to a pale yellow; this color becomes deeper until at 15°C. it is orange; at 20°C. the liquid boils and forms a reddish brown vapor. The color of this vapor becomes deeper, until at 40°C. it is a dark chocolate brown; at 140°C. it is black. The change of state consists in the relative preponderance of one or other of the two forms of the dioxide.

In whatever molecular form the dioxide is inhaled, it is at once altered to that corresponding to body temperature. At 40°C. approximately 30 per cent of the dioxide is in the form of NO_2 and 70 per cent at N_2O_4. It is in this proportion that the gases act upon the respiratory tract.

Nitrogen dioxide in the form of N_2O_4 reacts with water to produce nitric and nitrous acid in accord with the equation:

$$N_2O_4 + H_2O = HNO_3 + HNO_2$$

The dioxide in the form NO_2 reacts with water and oxygen from the air to produce nitric acid and nitric oxide according to the equation:

$$3NO_2 + H_2O = HNO_3 + NO$$

The nitric oxide formed is then oxidized and converted into nitric acid.

The decomposition of 1 milligram of nitrogen peroxide reaching the respiratory tract yields 0.55 milligram of nitrous acid and 0.98 milligram of nitric acid. These acids react with the alkali in the tissues of the respiratory tract and in so doing exert their irritating action. The neutralization results in the formation of nitrates and

nitrites, chiefly the sodium salts. The former has no physiological significance, but the nitrite when absorbed exerts a systemic action. For each milligram of the dioxide acting upon the respiratory tract, 0.75 milligram of sodium nitrite is formed. The inhalation of the maximum allowable concentration of nitrogen dioxide not inducing severe effects, 39 parts per million parts of air, over a period of one hour would result in the absorption of approximately 20 milligrams of sodium nitrite. (This is figured on an effective pulmonary ventilation of 6 liters and complete absorption.) Higher or lower concentrations in the inspired gas may result in the absorption of proportionately greater or lesser amounts of the nitrite.

The sodium nitrite produced from nitrous fumes, and then absorbed from the surface of the respiratory tract, produces the same systemic action as when sodium nitrite is swallowed. The arteries are dilated, the blood pressure falls and vertigo and headache follow; in large amounts the nitrite also alters the hemoglobin to methemoglobin. The systemic action of the nitrites does not, however, play an important part in poisoning by nitrous fumes; for after exposure to high concentrations the irritation of the respiratory tract is so intense that it obscures the systemic action. In men frequently exposed to low concentrations of nitrous fumes the rapidly acquired habituation to sodium nitrite prevents the development of systemic effects. Habituation in this respect does not, however, render their lungs less sensitive to irritation.

Nitrogen dioxide is evolved when nitric acid acts upon organic material; and this occurs particularly when the acid is spilled during its storage or shipment; for the acid then attacks wooden floors, refuse, or any organic material in its path with evolution of the red fumes. Nitric acid is also decomposed into the dioxide by heat even in the absence of organic material. Numerous organic substances containing the nitrous radicle give off nitrogen dioxide when burned. Celluloid and related products, gun cotton, and dynamite are examples of this class of materials. Relatively small amounts of the oxide result from the explosion of dynamite, but considerable quantities are produced when it is burned without exploding. Nitrogen dioxide also occurs as a waste or intermediary in numerous processes of chemical manufacture employing nitric acid.

The nitrous fumes are the most insidious of all the irritant gases. After the burning or incomplete explosion of dynamite in a tunnel, or the spilling of nitric acid on a wooden floor, or some similar slight mishap, a workman inhales some of the fumes for a time, but is little inconvenienced. He goes home and eats his supper feeling perfectly well. During the night edema of the lungs develops and before noon,

or even before morning he is dead, drowned in the volume of fluid poured out in his lungs.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF NITROUS FUMES.

	Parts of Nitrogen Dioxide per Million Parts of Air
Least amount causing immediate irritation to the throat [14]	62
Least amount causing coughing [14]	101
Maximum concentration allowable for prolonged exposure [14]	39
Dangerous for even short exposure [14]	117 to 154
Rapidly fatal for short exposure [14]	240 to 775

[14] Lehmann, K. and Hasegawa, Arch. f. Hygiene, 1913, LXXVII, 323.

Ozone.

Ozone is a gas of very low solubility, but intensely irritating. Its point of acute action is in the lungs.

Phosgene.

Phosgene is a colorless gas of specific gravity 1.43, which fumes in moist air as a result of partial conversion into hydrochloric acid. The gas is used to a limited extent in the dye industry, where it is handled in the liquid state in steel cylinders. The main source of phosgene as a contaminant of the air is from the decomposition of chloroform and carbon tetrachloride by heat.

The danger of using chloroform in the presence of an open fire or a gas flame has long been recognized by anesthetists; but the use of indirect heating and electric illumination, and even better the disuse of chloroform as an anesthetic because of its own poisonous character, have largely removed the danger from this source. Carbon tetrachloride, however, has come into extensive use as a fire extinguisher, and also as a noninflammable cleaning agent. The tetrachloride appearing on the market is often disguised by the addition of odorous substances or mixed with small amounts of chloroform or petroleum to prevent freezing and is then sold under various trade names such as "carbona" and "pyrene."

In experiments conducted by the United States Bureau of Mines,[1] carbon tetrachloride was sprayed on heated iron or an excelsior fire in a gas tight room of 1,000 cubic feet capacity. The use of 0.3 to 1.0 liter of the tetrachloride resulted in the contamination of the air in the chamber with phosgene to the extent of 15 to 168 parts per million parts of air. This is equivalent, under the conditions, to a production

[1] U. S. Department of Interior, Bureau of Mines, Technical Paper 248, 1921.

of 0.4 to 4.5 liters of phosgene. A number of fatalities from phosgene poisoning have resulted from the use of carbon tetrachloride fire extinguishers in confined places such as mines or inside of buildings.

In the presence of moisture phosgene decomposes with liberation of hydrochloric acid according to the equation:

$$COCl_2 + H_2O = 2HCl + CO_2$$

The irritant action of phosgene is supposed to arise from the hydrochloric acid liberated in the moisture upon the surface of the respiratory tract; but it is much more toxic than the equivalent concentration of free hydrochloric acid. Its action is exerted largely upon the deeper respiratory structures. The free hydrochloric acid from the small portion of the phosgene which decomposes in the air irritates the upper respiratory tract.

In its slight immediate effects and subsequent virulent results phosgene resembles the nitrous fumes. In industry fatal exposure to it is rather rare, except as an incident of the use of fire extinguishers. It is one of the principal gases used in war.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF PHOSGENE.

	Parts of Phosgene per Million Parts of Air
Least detectable odor[1]	5.6
Least amount required to cause immediate irritation to the eyes[1]	4.0
Least amount required to cause immediate irritation to the throat[1]	3.1
Least amount required to cause coughing[1]	4.8
Maximum concentration allowable for prolonged exposure[1]	1.0
Dangerous for even short exposure[1]	25
Rapidly fatal	over 25

[1] U. S. Department of Interior, Bureau of Mines, Technical Paper 248, 1921.

Phosphorus Trichloride and Pentachloride.

Phosphorus trichloride is a colorless liquid which boils at 76°C. Its vapors decompose in the presence of moisture with the liberation of hydrochloric and phosphorus acids according to the reaction:

$$PCl_3 + 3H_2O = H_3PO_3 + 3HCl$$

The action of phosphorus trichloride is similar to that of phosgene. The vapor, however, decomposes to a greater extent in the air. For that reason it is more irritating to the upper respiratory tract than is

phosgene, but it acts less severely upon the lungs. Its action combines the properties of the irritants of both subgroups 1 and 3.

Phosphorus pentachloride (PCl_5) is similar in behavior to the trichloride. The only toxic concentration recorded is for mice; 120 parts per million of air kills them after 10 minutes' exposure.

So far as known systemic poisoning does not occur.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF PHOSPHORUS TRICHLORIDE.

	Parts of Phosphorus Trichloride per Million Parts of Air
Maximum concentration allowable for prolonged exposure [11]	0.7
Maximum concentration allowable for short exposure [11]	2 to 4
Dangerous for even short exposure [11]	50 to 90
Rapidly fatal for short exposure [11]	6520

[11] Kobert, R., Kompendium d. prakt. Toxicol., Stuttart, 1912.

Arsenic Trichloride.

Arsenic trichloride is a colorless liquid boiling at 134°C. Its vapors decompose in the presence of moisture with the liberation of hydrochloric acid and arsenious oxide according to the reaction:

$$2AsCl_3 + 3H_2O = 6HCl + As_2O_3$$

The action of arsenic trichloride is similar to that of phosphorus trichloride.

The only toxic concentration for the trichloride reported in the literature is for mice; 338 parts per million of air killed these animals after an exposure of 10 minutes.[1]

So far as known systemic poisoning from absorption of the arsenic in this gas is not a considerable factor in its effects; but the possibility must be kept in mind.

Subgroup IV. Hydrocarbons.

All of the gases of the three subgroups dealt with above are characterized (a) by strong irritant action, and with the exception only of hydrogen sulfide by no other considerable effect, and (b) by alteration or destruction of the gas as an essential feature of the chemical reaction with the first tissue with which the gas comes in contact.

In contrast, the gases of subgroup IV are not destroyed or altered during absorption, and while they have more or less marked irritant

[1] U. S. Department of Interior, Bureau of Mines, Technical Paper 248, 1921.

effects in the respiratory tract, these symptoms are of less importance than those induced by the action of the substances after absorption into the blood. As the solubility of these substances is low, they should act upon the deeper parts of the lungs; in fact, however, they are absorbed so actively from the alveolar region of the lungs that the concentration there is kept low. The main damage occurs in the bronchi and bronchioles.

Substances of this type are the fatty hydrocarbons, their alcohols, ethers and halogen substitution products. Their general effects will be discussed under anesthetics in chapters X, XI and XII.

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(See also bibliography at the end of previous chapter.)

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Chapter X.

Group III. Volatile Drugs and Druglike Substances. Anesthetics.

All the volatile hydrocarbons and one noncarbonaceous gas have the property of inducing anesthesia when they are inhaled in sufficiently high concentration. But they differ both in the intensity of their anesthetic action and in their accessory effects; some are much more injurious than others. They differ from one another even more markedly in the chronic poisonings induced by prolonged exposure to low concentrations. Repeated slight exposures, or in some cases even a single severe exposure to one or another of them, especially one of the more toxic subgroups, may elicit special types of symptoms and induce equally characteristic post-toxic pathological changes in the various tissues, differing according to the particular hydrocarbon inhaled.

Classification.

These gases may be classified under six subgroups according to their characteristic chemical, physical and especially their physiological properties.

Subgroup I. Anesthetic gases without serious after effects: nitrous oxide, hydrocarbons of the fatty series, ethers, aldehydes, ketones, ethereal salts of organic acids.

Subgroup II. Anesthetic gases causing organic changes mainly in visceral organs: halogen derivatives of the fatty hydrocarbons.

Subgroup III. Anesthetic gases causing organic changes mainly in the hematopoietic system: hydrocarbons of the aromatic series.

Subgroup IV. Anesthetic gases causing organic changes mainly in the nervous system: alcohols, sulfur derivatives of fatty hydrocarbons.

Subgroup V. Organic nitrogen compounds whose chief action is on the blood and circulation.

Action of Anesthetic Gases.

The anesthetic gases are characterized primarily by their depressant effect upon the activity of the central nervous system. They are carried to the brain and spinal cord in solution in the blood. The volume of

blood flowing thru the nervous system is so large that the partial pressure of any gas contained in the blood rises almost immediately to the same pressure in the nervous tissue. As we have seen in Chapter V, the pressure of each gas in the arterial blood as it leaves the lungs is in equilibrium with the pressure of that gas in the air of the lungs. Thus for all gases of this class the partial pressure of the gas in the brain is almost immediately the same as that in the lungs. The concentration in the brain depends upon the solubility of the gas in this tissue and upon the partial pressure; the concentration varies therefore in proportion to the partial pressure of the gas in the lungs. The effective concentration is probably that in the lipoids of the nervous tissue, rather than in the brain as a whole; but the vapor pressures would be the same, and the concentrations therefore proportional.

The degree of the anesthetic effect of each gas depends both upon the (effective) concentration in the brain and upon its own specific pharmacological activity. According to the Meyer-Overton theory (see below) the specific activity is the same for all anesthetics: the degree of effect would then be proportional simply to the molar concentration. Thus for substances of high solubility in lipoids correspondingly low partial pressures would be anesthetic.

With all anesthetic gases the effects pass thru a series of stages as the partial pressure of the gas in the lungs is increased from a lower to a higher intensity. The following is a brief outline of the various stages that may be observed:

Stages of Anesthesia.

In what may be termed the preliminary stage of anesthesia the low pressure of the gas in the lungs and blood and the proportionally low concentration in the central nervous system merely decrease the accuracy of the coördination of the finer movements, and dull sensation. Skilled work is performed more slowly, and more errors occur, than when the individual is in normal condition.

In the next stage somewhat higher concentrations in the blood cause confusion of ideas and bewilderment. Muscular coördination is seriously disturbed; the man is somewhat "drunk."

In the third stage (termed the first stage of surgical anesthesia) higher pressures in the lungs and higher concentrations in the brain generally induce excitement; but the degree of excitement is variable and with some anesthetics may be almost or entirely absent. With those anesthetics which induce excitement the condition is largely the result of loss of functional control and particularly loss of inhibition; so that the centers of motion are set free and act more strongly than when they are under their normal regulation. Excitement from this

cause varies widely from one man to another. In addition to this excitement some anesthetic gases, notably the higher members of both the methane and aromatic series, stimulate the cortex of the brain and induce convulsive muscular movements, twitchings and writhings.

In the fourth stage (corresponding to the second stage of surgical anesthesia) still higher concentrations of the anesthetic gases induce complete unconsciousness and immobility. In the lowest concentrations sufficient to induce unconsciousness the muscles maintain their tonicity and with some anesthetics even exhibit a hypertonicity, but as the concentration rises they relax. The face then assumes a calm, deathlike appearance. The reflexes disappear; one of the last to go is the closure of the eyelid when the cornea is touched.

The final stage is reached when the concentration of the anesthetic in the blood abolishes the activity of the respiratory center. The extent to which the concentration in the blood can be raised above that necessary to induce unconsciousness without danger of respiratory failure varies with the different anesthetics. With some the margin is wide, but with others death results from even a slight increase in the concentration beyond that of unconsciousness. Death is due to the paralyzing action of the anesthetic upon the respiratory center. The heart generally continues to beat for some minutes after breathing stops. Exceptions to this order of events occur only in a few special cases, particularly with chloroform and related substances, when the heart may stop first.

Pharmacological Activity.

The pharmacological activity of an anesthetic is estimated by the concentration in the blood necessary to elicit any particular degree of effect. Comparison of the various anesthetics is usually made upon the basis of the concentration in the arterial blood necessary to induce unconsciousness. Wide differences are found. For example, a concentration of approximately 0.25 gram of chloroform per liter of blood causes unconsciousness; while 1.0 gram of ether, or 2.25 grams of ethyl alcohol are required to produce the same effect. It is important not to lose sight of the fact that the comparison of anesthetics is usually made upon the basis of the concentration in the blood, and not that in the air breathed, nor even the partial pressure of the gas in the air in the lungs. Solubility and volatility are both important factors in the action of the anesthetic hydrocarbons.

Volatility and Solubility.

A substance of low volatility produces at most only a low partial pressure of vapor, and for this reason inhalation of it may have little

physiological effect. A substance of low solubility is absorbed into the blood only in correspondingly low concentration. Thus unless the pharmacological activity of the substance is high, its low volatility and low solubility may deprive it of appreciable physiological effect. Contrariwise high volatility and high solubility may afford a high physiological effectiveness even for a substance of low inherent pharmacological action.

Any anesthetic substance present in the blood in sufficient quantities will produce a high, or even fatal, degree of anesthesia; many of the anesthetics, however, because of their low solubility, are unable to reach the blood in a quantity sufficient to elicit more than a feeble response. For example, decane is by all indications a more powerful substance pharmacologically than is pentane; decane has, however, an extremely low solubility in blood, while pentane is much more soluble. Therefore, when the two gases are inhaled in equal amounts, the feebler pentane induces the greater anesthetic action because its solubility allows the concentration in the blood to rise to a point which more than compensates for its weaker pharmacological activity as compared to decane. The higher members of the paraffin series are inert by reason of their insolubility.

Solubility not only plays a part in limiting the action of an anesthetic, but contributes as well to the character of its action. Soluble anesthetics are absorbed rapidly (when the amounts are expressed by weight, not as percentages of saturation) and eliminated slowly; their action is therefore prolonged as in the case of methyl alcohol. The rate of volatilization of equal quantities of various vapors from their solution in water or blood varies inversely as their solubility. Relatively insoluble anesthetics are eliminated rapidly, for a high pressure of the vapor in the air is necessary to hold them in solution. The part played by solubility in the absorption and elimination of gases and vapors has been discussed in Chapter V.

The volatility of a fluid limits the concentration which its vapor can attain in the air, and therefore limits its physiological action. Decane used in the illustration above has a vapor pressure of 2.7 mm. at 20°C.; the maximum concentration of the vapor which can exist in the air at this temperature is 3,550 parts per million while at body temperature the maximum concentration in the air is 10,000 parts per million. Neither of these concentrations would cause death.

Chemical Structure and Pharmacological Activity.

The complexity of the chemistry of the living body is too great to permit complete formulation of this relation in the present state of

knowledge, but certain generalizations can be made of the chemical structures of the anesthetics and their pharmacological activity.

As a rule in any homologous series of the hydrocarbons the higher members have a greater pharmacological activity than the lower members. Thus propane and butane produce unconsciousness when present in the blood in a lower concentration than methane or ethane; amylene is more active than ethylene. This relation applies likewise to their alcohols; thus the activity of the simple alcohols rises from methyl alcohol thru ethyl, propyl and butyl to amyl alcohol, which is the most powerful of the series. In the same way xylene is more active than benzene. On the other hand, when the hydroxyl groups of the alcohols are increased, as in the series ethyl alcohol, glycol, and glycerol (glycerine) the activity is progressively diminished.

The presence of the carboxyl group (COOH) generally prevents any anesthetic activity. Replacing the H of the carboxyl group with a radical of one of the fatty hydrocarbons to form an ethereal salt restores the anesthetic action, but only in a low degree. Acetic acid has no anesthetic properties, but ethyl acetate is mildly anesthetic.

The substitution of a halogen for a hydrogen of the fatty hydrocarbons greatly increases the anesthetic activity. Furthermore the compound becomes less specific in its action and affects tissues other than the nervous system. In many instances it alters and injures them organically. Chloroform (trichloromethane) is much more active pharmacologically than methane, and in addition has toxic properties which may cause degeneration of the heart muscle, liver, and kidneys.

The aldehydes of the fatty hydrocarbons are anesthetic in their action, but the lower members of the series are irritating to the surface tissues of the respiratory tract to such an extent that their anesthetic action is largely obscured.

Many of the esters of the fatty hydrocarbons fail to exhibit their anesthetic action because they contain more active radicals. Thus ethane (C_2H_6) is an anesthetic; but ethyl nitrite ($C_2H_5NO_2$) cannot be so classed, because the NO_2 radical has a powerful and entirely different effect which forces the narcotic action into the background.

The physical properties of the anesthetics, particularly their solubilities, as shown above, are even more closely related to their pharmacological activity than is their chemical structure; it is often difficult to tell whether in the physiological action the determining factor is physical or chemical, for the two generally run parallel. As a rule the hydrocarbons least soluble in water and most soluble in fats and fatlike substances have the greatest pharmacological activity. This generalization has been elaborated by Meyer and Overton, who have compared the pharmacological activity of anesthetics with the relative

solubility of the various substances in oil and water. The activity increases in general with the coefficient of partition: $\frac{\text{Solubility in oil}}{\text{Solubility in water}}$.

Theories of Anesthetic Action.

The action of the anesthetic hydrocarbons is exerted directly upon the nervous tissue; the phenomena of anesthesia are induced thru this specific action, and do not arise secondarily from alteration in such bodily functions as respiration or circulation. Beyond this point the fundamental action of the anesthetics is a matter of speculation. Numerous theories have been advanced, but probably no one of them affords a complete explanation of the action. These theories, nevertheless, indicate the trend of present ideas upon the subject and for that reason the more important are given here.

(1) Claude Bernard and later Verworn pointed out the similarity of the symptoms of anoxemia and anesthesia. Verworn believed that narcosis is due to inhibition of the oxidative activity of the nerve cells by the anesthetic. This diminution of oxidation may be induced in the same manner that certain catalytic substances are poisoned by the hydrocarbons. It is difficult in this conception to differentiate cause and effect; it is uncertain whether the diminution of oxidation is the cause or the result of the anesthesia.

(2) Meyer and Overton suggest that the anesthetics act upon the lipoids of nerve cells, rendering them more fluid, and thus changing their relation to the other constituents of the cells. The derangement of the physical condition of the cells impairs their function and narcosis results. These authors have shown that the pharmacological activity of the various anesthetics corresponds in general to their differential solubility in oil and water.

(3) Lillie has suggested that the essential feature of narcosis is physical, and that it consists in a diminished permeability of the cell membrane to ions; when ions can no longer penetrate, vital activity ceases.

(4) Moore and Roaf conclude that the action is chemical. In their view the anesthetics form unstable compounds with the protein of the tissue cells; anesthesia is due to the paralysis of the chemical activity of the protoplasm resulting from this combination.

(5) Still another view is based on the anatomical structure and peculiarities of the junctions, termed synapses, of nerve cells, or neurones. Under the action of the anesthetics the synapses between neurones are altered so that the passage of impulses from one cell to another is impeded. This conception is analogous to that of a telephone

or other electric switchboard (which in fact the nervous system much resembles) under conditions of impaired connections.

This much is clear: the anesthetics exert their main action upon those tissues in which sensitivity is most highly developed. But the manner in which they interfere with the functions of these tissues is still unknown. The abolition of function follows in reverse order the evolutionary development of the various classes or levels of nerve centers. Thus the higher centers, those concerned in consciousness, voluntary motions and sensations, are affected first and most intensely; the basal centers, controlling arterial pressure, respiration and other involuntary functions are affected last, and then only by relatively high concentrations of the anesthetics.

Chronic Poisoning.

An outstanding feature of anesthesia, as ordinarily seen, is the fact that the removal of the anesthetic from the blood restores the nervous system to its original activity without any appreciable damage. Such is the case only within limits, however. Probably any anesthetic substance acting for a sufficient length of time will induce organic changes within the body. It is these more slowly developing organic changes, rather than the immediate anesthetic effects, which characterize chronic poisoning by the hydrocarbons. Ethyl alcohol, altho ordinarily taken by way of the alimentary tract instead of the lungs, affords the commonest example of functional derangement passing in time into organic degeneration. Taken at infrequent intervals ethyl alcohol induces each time the typical phenomena of anesthesia; thus a single drink, while affecting conduct imperceptibly, may neutralize sensation sufficiently to overcome a considerable toothache. Drunkenness usually does not exceed the second stage of anesthesia as the stages are defined here. After such degree of anesthesia there is recovery with no apparent permanent damage. When, however, the ingestion of alcohol is frequent and some degree of anesthesia is thus maintained over a long period of time, characteristic organic changes develop, not only in nervous tissue, but also in such organs as the liver.

The different anesthetics vary widely in the facility with which they induce organic changes. Some have a definite selective poisonous action upon particular tissues. The hydrocarbons of the aromatic series induce changes in the hematopoietic (or blood-forming) system which result in anemia, hemorrhages and loss of white cells. The hydrocarbons of the fatty series, on the other hand, are so slow in inducing organic changes that it is doubtful if definite examples of their action in this direction have been observed. The halogen derivatives of the fatty hydrocarbons are, perhaps, the most active of all in

causing organic changes; their main poisonous action is upon the heart and upon the liver. The organic effects may result even after short exposure; a single anesthesia by means of chloroform is sometimes followed by death from degeneration of the liver. The alcohols, notably methyl, cause organic changes in the nervous system, while the sulfur derivative, carbon disulfide, exerts this action upon the nervous system to a high degree. The action of the anesthetic hydrocarbons as protoplasmic poisons is the basis of the classification in the first section of this chapter.

Irritant Action.

Many of the anesthetic gases and vapors exert an irritant action upon the surface tissues of the respiratory tract. In some cases the irritant action largely obscures the anesthetic action. This is particularly true in the case of the aldehydes, which are therefore listed in the general classification as irritants rather than as anesthetics. The alcohols likewise have irritant properties, probably thru their dehydrating action upon the tissues. The lower members of the paraffin series are not irritating, but the higher members are to some extent. So also are the ethereal salts, particularly those of organic acids. These salts are broken down by contact with water with the formation of alcohol and the liberation of the acid; the irritation is induced by the products of this hydrolysis. Their action as irritants is discussed in Chapter VIII and the last section of Chapter IX.

Treatment of Acute Poisoning.

The essential points in the treatment of acute poisoning by the anesthetic gases are first to keep the patient alive until the anesthetic in the blood is eliminated, and second to get it eliminated as quickly as possible. Death usually results from paralysis of the respiratory center; the heart, with a few exceptions, chiefly from the halogen compounds, continues to beat for several minutes after breathing has stopped. The course of treatment is the same as that for carbon monoxide poisoning, as described in Chapter VII. It consists in the administration of oxygen and 5 per cent carbon dioxide. If natural breathing has ceased the most effective means of restoration is artificial respiration, preferably by the prone pressure method, combined with inhalation of oxygen and carbon dioxide. The patient should be kept warm, and after recovery of consciousness, absolutely at rest. Nothing should be administered by mouth until the patient is fully conscious. Hypodermic medication should be avoided, except when some physical injury requires morphine to overcome pain after termination of anesthesia.

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Chapter XI.

Group III (continued). Volatile Drugs and Drug-like Substances.

Subgroup I. Anesthetics Without Serious After Effects.

This subgroup includes both those substances which are used as anesthetics in surgery, and also a large number of related substances which occur in industry, but which owing to some disadvantageous feature are not used in surgery. The surgical anesthetics have their own extensive literature and will be only briefly referred to here, so as to leave space for the less well known effects of substances of toxicological importance in industrial medicine.

Hydrocarbons of the Paraffin Series: Gasoline, Naphtha and Benzine.

The hydrocarbons of the paraffin series are encountered almost exclusively as products of petroleum. Except methane, the "fire damp" of coal mines, these hydrocarbons are rarely found singly, but occur as mixtures. They are the lighter products of petroleum distillation.

Fuel oil and lubricating oil, which are essentially petroleum from which the more volatile constituents have been removed by fractional distillation, do not require consideration here; for only the lighter constituents are sufficiently volatile to give rise to toxic contamination of the air at ordinary temperatures. The vapors arising from crude petroleum at ordinary temperatures consist of these more volatile substances.

The gas coming from oil or gas wells consists chiefly of hydrogen, methane and ethane. The liquid pumped out of the wells still retains a quantity of ethane and heavier gases in solution. When the petroleum is distilled, the ethane, propane and buntane are evolved in the gaseous state; they are then collected and compressed. The liquefied portion is known as cymogene and is used as a refrigerating agent. A slightly higher fraction consisting largely of butane and pentane is likewise liquefied and distributed as fuel for gas stoves. The hydrocarbons in

both of these mixtures have only slight toxic action, except in high concentrations.

Hydrocarbons of the Methane Series.

Name	Formula	Boiling Point of Normal Isomeres ° C.	Physiological Action
Methane	CH_4	— 160.	Simple Asphyxiants
Ethane	C_2H_6	— 85.4	
Propane	C_3H_8	— 37.0	Anesthetic
Butane	C_4H_{10}	10.	
Pentane	C_5H_{12}	37.	Anesthetic Convulsive Irritant
Hexane	C_6H_{14}	69.	
Heptane	C_7H_{16}	98.	
Octane	C_8H_{18}	124.	
Nonane	C_9H_{20}	148.	
Decane	$C_{10}H_{22}$	168.	

Higher homologues of this series are not sufficiently volatile to exert physiological action under ordinary conditions. The members of the series from $C_{16}H_{34}$ upward are solids at body temperature.

As originally applied, the name gasoline was synonymous with petroleum ether and first run gasoline. Prior to the employment of internal combusion engines, gasoline was an undesirable product which it was necessary to separate from the distillates to render them safe to use for illuminating purposes. The great demand for gasoline for motor cars makes gasoline now the most valuable product of petroleum distillation. In order to supply the demand for gasoline, petroleum ether has been replaced upon the market by a less volatile product containing, beside petroleum ether, considerable amounts of naphtha and benzine.

In an increasing proportion of the gasoline now sold the products of petroleum distillation are blended with light hydrocarbons from other sources. For this purpose the distillation products from coal, from oil shale and from cracked petroleum are used. These products contain cyclic compounds, substances with delayed effects in addition to those of the paraffin series. In order to increase the volatility of such mixtures "casing head" gasoline is added. "Casing head" gasoline consists principally of butane, and is obtained by condensing it from natural gas.

Thus there are wide variations in the components of commercial gasoline. Naphtha and benzine may be classed physiologically with gasoline, but are less varied in composition. They are inherently more

toxic than the lighter fraction of gasoline, but as they are also less volatile they are not so readily inhaled. They are largely used for dry cleaning, grease extraction, and in paint as a substitute for turpentine. Benzine should not be confused with the cyclic compound benzene, or, as it is often spelled, benzol.

The relations of the principal fractions obtained from petroleum on distillation are as follows:

Distillation Fractions of Petroleum.

Name of Product	Boiling Point, ° C.	Main Constituents	
Petroleum ether or first run gasoline	40 to 90	Pentanes and hexanes.	Range of constituents sold as commercial gasoline.
Naphtha	90 to 120	Hexanes, heptanes and octanes.	Used in dry cleaning and as substitutes for turpentine.
Benzine	120 to 150	Octanes and nonanes.	
Kerosene	150 to 300	Nonanes, decanes and higher hydrocarbons.	Not sufficiently volatile under ordinary conditions to cause toxic effects.
Lubricating oils	Above 300		

The distillation products of coal are now used to only a limited extent in blending certain gasolines, but this use is rapidly increasing. Their chief constituent is benzene (C_6H_6), but smaller and variable amounts of toluene and xylene are also present. Coal distillate is added to gasoline in amounts varying from over 90 per cent, which makes the mixture really a commercial grade of benzene, down to less than 20 per cent. Gasoline mixtures containing benzene are usually easily recognized by the characteristic odor of the coal tar hydrocarbons; they have also a relatively low specific gravity, altho their average boiling point corresponds to that of high test gasoline. Benzene is more toxic than gasoline. (See Chapter XII.)

Besides benzene, other organic substances have been added to various gasolines as antidetonants in order to prevent the so-called "knocking" under high compression. The most important of these components are lead tetra-ethyl (see page 185), aniline, and nitrobenzene.

For the drivers of motor cars poisoning by gasoline rarely constitutes a hazard, altho as a result of incomplete combustion in the engine gasoline vapor may appear in the exhaust gas. This results from too rich mixtures of gasoline with air, owing to faulty adjustment of the carburetor or from failure of the gasoline vapor to ignite; the

condition termed "missing" cylinders. The idea that the toxicity of motor exhaust is due to unburned gasoline is entirely fallacious; for the gasoline concentration in the exhaust gases, even at the highest point attainable, never approaches in toxicity the carbon monoxide present even when this substance is at the lowest amount. It is carbon monoxide which gives to exhaust nearly all of its poisonous character. The mistake has probably arisen from the common observation that the exhaust gases are most toxic during the warming up of the engine, or when a very rich mixture is used, at which times the exhaust smells strongly of unburned gasoline. The point is overlooked that under such conditions the carbon monoxide content is also at its highest. It is possible also for the exhaust to be rich in carbon monoxide, but with little odor of gasoline. The uncombusted gasoline in exhaust gas is neither the cause nor even a reliable index of its poisonous character. Neither is the amount of smoke; for it is usually due to the partial volatilization and partial combustion of an excessive supply of the lubricating oil. (See carbon monoxide, Chapter VII.)

Men employed in the care and repair of automobiles are subject to gasoline fumes to a greater extent than are the drivers. Gasoline spilt in confined quarters or in low places, such as the pit in a repair shop floor during the draining of a gasoline tank, occasionally reaches a toxic concentration. The washing of automobile engines with gasoline, sometimes employed as a spray, in confined buildings may likewise occasionally cause poisoning. This is particularly true if the engine is cleaned while warm. The danger from fire during this procedure, however, greatly outweighs the chance of poisoning.

Toxic concentrations of gasoline vapors are occasionally encountered in confined quarters, as when gasoline leaks from storage tanks and pumping machinery, or is accidentally spilled in the underground pipe rooms of gasoline storage and dispensing stations. These conditions involve, however, an economic loss, and for that reason are prevented or soon corrected.

Men employed in cleaning the interior of tank cars or storage tanks, which have contained gasoline or crude oil, are particularly liable to poisoning, unless precautions are taken to remove as nearly as possible all the volatile matter and to insure a supply of uncontaminated air to the men. To remove all the liquid and vapor from such tanks, even with the use of steam, appears to be difficult and uncertain, and fatalities frequently result; the rescuer also is often overcome. In such work hose masks should be compulsory (see Chapter XV).

Establishments engaged in cleaning clothing by so-called "dry cleaning" use considerable amounts of gasoline, naphtha or benzine to extract grease from the fabrics. The hydrocarbon is used hot and is

later redistilled for purification. Unless precautions are taken to prevent the vapors from escaping from the heated liquid, they may readily give rise to poisoning. This may occur also in the distillation of naphtha, which is used for the extraction of oleaginous matter from garbage and other industrial residues. Poisoning by petroleum vapors occurs occasionally also in men entering sewers into which gasoline, benzine or naphtha has been run as a waste from garages, or from cleaning or extracting plants. Plants of this sort should be required to install well vented traps to catch all such liquids and prevent their reaching the common sewer.

The higher petroleum distillates, notably benzine, have an increasing application as substitutes for turpentine in quick drying paints. Numerous cases of poisoning now occur from paints containing these hydrocarbons, when they are used in close and ill ventilated quarters or applied to warm metal surfaces. Death has resulted from a few hours spent in painting the inside of a large water tank with such paint, and the victim has only headache and nausea as an insufficient warning of his danger. Benzine, naphtha and occasionally gasoline are used as solvents in the manufacture of rubber goods, especially in the dipping and drying procedures; and intoxication occurs unless the ventilation is arranged to prevent the inhalation of vapors. The light petroleum hydrocarbons have many uses in industrial procedures, such as removing grease or oil from machinery, cleaning of printers' type, and other occasional applications; but in such conditions poisoning is rare.

The striking feature of acute gasoline poisoning is the severe muscular jactitation occurring during the stage of excitement. In some cases the muscular movements are as violent as in an epileptic convulsion; they are particularly marked during the recovery in fresh air. With vapors of this type there is only a narrow margin between the concentration which produces anesthesia and that which causes death.

Physiological Response to Various Concentrations of Gasoline Vapor.[1]

	Parts of Gasoline Vapor per Million Parts of Air
Least detectable odor	300
Concentration dangerous for even short exposure	11,000 to 22,000
Rapidly fatal for short exposure	24,300

[1] U. S. Department of Interior, Bureau of Mines, Technical Paper 272, 1921.

Hydrocarbons of the Olefine Series.

The lower members of the olefine series are present in small amounts in coal gas, but they have no toxicological significance in such low

concentrations. Ethylene and propylene are used to induce surgical anesthesia; but they are effective only in high concentrations, 60 per cent or more, and for that reason are always administered with oxygen. Both of these substances when mixed with air act rather as simple asphyxiants than as anesthetics. The high concentration necessary to induce a marked physiological effect dilutes the oxygen of the air to a level which will not support life; thus 60 per cent in air reduces the oxygen to 8.4 per cent. When mixed with oxygen, or even with air in certain proportions, these gases are explosive.

The higher members of the series have a much stronger anesthetic action than ethylene and propylene, as is the case with the paraffins, but at present they are little used, altho amylene has been employed for surgical anesthesia. The principal substances in this series are as follows:

Hydrocarbons of the Olefine Series.

Name	Formula	Boiling Point of Normal Isomeres, ° C.	Physiological Action
Ethylene	C_2H_4	— 103	Simple Asphyxiant and Anesthetic.
Propylene	C_3H_6	— 37	
Butylene	C_4H_8	— 5	
Amylene	C_5H_{10}	35	
Hexylene	C_6H_{12}	70	
Heptylene	C_7H_{14}	100	

Hydrocarbons of the Acetylene Series.

Acetylene gas is the only hydrocarbon of the acetylene series of practical importance. The higher members of the series are encountered in small quantities in coal gas. Acetylene is extensively employed in welding and to a less extent for illuminating in localities unequipped with coal gas or electricity. The gas is generated by the action of water on calcium carbide, and is either made at the place of use or supplied from central stations in steel cylinders in which the compressed gas is held in solution in acetone.

Acetylene has sufficiently strong anesthetic properties for it to be used for surgical anesthesia. Forty per cent or more of the gas mixed with oxygen is used for this purpose. But as with ethylene and propylene it must be administered with oxygen; otherwise it acts as an asphyxiant.

Commercial calcium carbide frequently contains calcium phosphide as an impurity, and as a result the acetylene generated is contaminated with phosphene. (See page 188.) The percentages of phosphene that have been found range from 0.04 to 0.06 per cent.

HYDROCARBONS OF THE ACETYLENE SERIES.

Name	Formula	Boiling Point, °C.	Physiological Action
Acetylene	C_2H_2	—81.5	Simple Asphyxiant and Anesthetic.
Allylene	C_3H_4	—23.5	
Crotonylene	C_4H_6	27.5	

Ethers.

Ethyl ether is extensively used as a general anesthetic for surgical operations. It is also employed in the manufacture of smokeless powder and pyroxylin. Among those engaged in these industries a mild degree of ether intoxication is occasionally seen. It is followed by loss of appetite and headache.

Ether in high concentration is irritating to the respiratory tract and pneumonia sometimes follows its use as a surgical anesthetic when unskillfully administered. It is said to be somewhat irritating to the kidneys also; but organic degenerations are rarely caused by ether.

The inhalation of a concentration of 35,000 parts of ether per million of air leads to unconsciousness if continued for 30 to 40 minutes. Higher concentrations produce unconsciousness in a shorter time, and very high concentrations cause death by failure of respiration if the inhalation is at all prolonged. The concentration requisite in the arterial blood for the production of surgical anesthesia is between 1.5 and 3.0 grams per liter. The coefficient of distribution for ether between the air of the lungs and the blood is 15.

ETHERS.

Name	Formula	Boiling Point, °C.	Physiological Action
Methyl Ether	$CH_3—O—CH_3$	21	Anesthetic and slightly irritant.
Ethyl Ether	$C_2H_5—O—C_2H_5$	35	
Propyl Ether	$C_3H_7—O—C_3H_7$	86	

Aldehydes.

The aldehydes have anesthetic properties, but their action in this respect is largely masked by the more intense irritant effect upon the surface tissues of the respiratory tract. The lower members of the aldehyde series possess a high solubility in water, and for that reason act primarily upon the upper respiratory tract; the higher members of the series, especially acrolein, are less soluble and act rather in the deeper parts of the respiratory tract. The aldehydes are discussed in more detail in the section devoted to the irritants (Chapters VIII and IX).

The aldehyde derivatives, methylal $CH_2(OCH_3)_2$, boiling point 42°C., and paraldehyde $(C_2H_4O)_3$, boiling point 124°C., do not have the irritating properties of the aldehydes, but are anesthetics.

It is stated that the prolonged inhalation of aldehydes occasionally leads to narcosis.[2 and 3] Because of their high solubility they are only slowly eliminated and if the exposure is repeated at short intervals they may accumulate in the body.

ALDEHYDES.

Name	Formula	Boiling Point, ° C.	Solubility in Water at 40° C.	Physiological Action
Formaldehyde	CH_2O	—21.0	Soluble	Primarily irritant but also anesthetic.
Acetaldehyde	C_2H_4O	20.8	Miscible in all proportions	
Propaldehyde	C_3H_6O	49.0	Slightly soluble	
Butaldehyde	C_4H_8O	74.0	Slightly soluble	
Acraldehyde (Acrolein)	C_3H_4O	52.0	Slightly soluble	

Ketones.

The ketones, unlike the aldehydes, are not markedly irritating to the respiratory tract. They have, however, besides their anesthetic properties, a marked stimulating action upon the respiratory center.

The vapor of acetone is more toxic for brief exposure than is that of chloroform, and is only slightly less toxic than that of benzol.[1] Acetone in a concentration of 20,600 parts per million of air kills mice after an exposure of 10 minutes; a similar result is reached with carbon disulfide in 17,700 parts, by benzol in 19,000 parts, and by chloroform in 25,900 parts. But this statement of relative toxicity applies only in regard to acute poisoning. Prolonged exposure to acetone vapor has not the destructive action upon the tissues exerted by the other substances here mentioned. Acetone in small amounts is found in the blood and expired air of men with diabetes and nephritis.

KETONES.

Name	Formula	Boiling Point, ° C.	Physiological Action
Dimethyl ketone (acetone)	$(CH_3)_2CO$	56.3	Anesthetic markedly stimulating to respiratory center.
Methyl-ethyl ketone	$CH_3COC_2H_5$	81.0	
Diethyl ketone	$(C_2H_5)_2CO$	103.0	

[1] U. S. Department of Interior, Bureau of Mines, Technical Paper 272, 1921.
[2] Brumnthaler, Zentralbl. f. Gewerbehygiene, 1914, II, p. 24.
[3] Loeb, Arch. f. exper. Path. u. Pharm., 1912, XLIX, p. 114.

Ethereal Salts of Organic Acids.

The addition of the carboxyl group (COOH) to the radicles of the fatty hydrocarbons destroys their anesthetic power. The combination of these fatty acids with hydrocarbons to ethereal salts restores this power to a limited degree. The vapors of these substances do not appear to have any specific poisonous action; but they are somewhat irritating to the membranes of the respiratory tract, probably from hydrolysis of the salt with the liberation of the acid. As the hydrolysis continues in the body, the alkali salts of the acids are formed, and are nontoxic. As the concentration of the alcohols produced is also insufficient to induce toxic effects, such anesthetic and other actions as are caused must be due chiefly to the undecomposed ethereal salt. The toxicology of the methyl salts has not been studied. Amyl acetate is the most extensively used of this class of compounds, and is employed as a solvent in lacquers, in various "dopes," and in paint removers. It is somewhat irritating to the eyes, upper respiratory tract, and bronchi. A concentration of 65,000 [4] parts of amyl acetate per million of air has been found insufficient to induce complete narcosis, and a concentration of 100,000 parts per million of air did not cause death.[5]

Ethereal Salts of Organic Acids.

Name	Formula	Boiling Point, °C.	Physiological Action
Methyl formate	CH_3CO_2H	32.3	Mildly Anesthetic. Irritating.
Methyl acetate	$CH_3CO_2CH_3$	57.5	
Methyl butanate	$CH_3CO_2C_3H_7$	102.0	
Ethyl formate	$C_2H_5CO_2H$	54.4	
Ethyl acetate	$C_2H_5CO_2CH_3$	77.0	
Ethyl butanate	$C_2H_5CO_2C_3H_7$	119.0	
Propyl acetate (Iso)	$C_3H_7CO_2CH_3$	35.8	
Butyl acetate (Iso)	$C_4H_9CO_2CH_3$	116.3	
Amyl acetate (Iso)	$C_5H_{11}CO_2CH_3$	148.0	

For Bibliography see end of Chapter X.

[4] Lehmann, K. B., Arch. f. Hyg., 1913, LXXVII, 260.
[5] Koelsch, F., Ztschr. d. Zentrastelle f. Volkswohlfahrt, 1912, XIX, 246.

Chapter XII.

Group III (continued). Volatile Drugs and Drug-like Substances.

Anesthetics Injuring Chiefly Visceral Organs.

The three subgroups of the anesthetic hydrocarbons next to be considered resemble the first subgroup, discussed in the previous chapter, in their immediate effects, but in general they are pharmacologically much more powerful. In addition they have the property of initiating serious and often fatal organic changes in various tissues and organs of the body.

Subgroup II. Halogen Derivatives of the Hydrocarbons.

The halogen compounds of the aliphatic hydrocarbons are more active pharmacologically than the hydrocarbons from which they are derived. This increased activity is not due to any action of the halogen on the tissues, but to the entire molecule of the substance. The chlorine derivatives are decomposed in the body to only a small extent; the iodine and bromine compounds with the methyl and ethyl groups are, however, more or less rapidly hydrolized into the corresponding alcohol or other hydrocarbon, and hydriodic or hydrobromic acid.

The halogen derivatives have a less specific action on nervous tissue than do most of the anesthetic hydrocarbons; their injurious effects involve a larger number of other tissues. This toxic action is particularly marked with the higher members of the series; it consists in a depressant action upon the heart, both weakening the cardiac muscle and disturbing coördination; it is sometimes fatal. Prolonged inhalation may induce degenerative changes in the heart, liver, kidneys, and occasionally the pancreas. Recovery from the anesthetic action may be complete, and yet a few days later death may result from these degenerative changes.

As a rule the toxicity of the chlorine derivatives of the hydrocarbons increases with the addition of each atom of chlorine to the molecule up nearly to complete replacement of hydrogen with chlorine; but diminishes slightly when the substitution is carried to the complete exclusion of hydrogen. Thus both carbon tetrachloride and methyl

chloride (CH_3Cl) are somewhat less toxic than chloroform. The hydrocarbon radicle also influences the toxicity; thus the chlorine derivatives of the paraffin series increase in toxicity in ascending the scale. These relations are illustrated in the following table:

TABLE OF COMPARATIVE TOXICITY OF CHLORINE DERIVATIVES OF THE ALIPHATIC HYDROCARBONS.

Relative lethal concentrations by volume in air, if toxicity of $CCl_4 = 1$.

Methyl chloride	CH_3Cl	0.6 (approximation)
Trichloromethane	$CHCl_3$[1]	2.2
Tetrachloromethane	CCl_4[1]	1.0
Dichloroethylene	$C_2H_2Cl_2$[2]	1.7—lethal for cats in 30 minutes
Trichloroethylene	C_2HCl_3[2]	1.7— " " " " " "
Perchloroethylene	C_2Cl_4[2]	1.6— " " " " " "
Tetrachloroethane	$C_2H_2Cl_4$[2]	9.1— " " " " " "
Pentachloroethane	C_2HCl_5[2]	6.2— " " " " " "

[1] Waller, A. D., Journ. Amer. Med. Assn., 1919, LIII, 9.
[2] Herrmann, G., Inaugural Dissertation; Würzburg, C. Fuchs, 1911.

Halogen Compounds of Methyl.

The monohalogen compounds of methyl, CH_3Br, CH_3I, and CH_3Cl, are reactive gases, for after absorption they are decomposed into methanol (methyl alcohol), which is nearly nonreactive, and the halogen acid. The acid then combines with the sodium of the blood to form the sodium chloride, bromide or iodide. The marked accumulative property of methanol and its destructive action upon the nervous system render these three methyl halides particularly poisonous. They do not themselves accumulate in the body and reach an equilibrium preventing further absorption, as in the case of nonreactive gases, but are decomposed with the production of methanol. Consequently methanol continues to accumulate in the body as long as the exposure persists. Thus severe poisoning by methanol results after prolonged exposure to concentrations of a methyl monohalide too small to exhibit the anesthetic action of the undecomposed substance. The symptoms are those of methanol poisoning. Their development may be slow and recovery delayed; there is usually intense excitement and even epileptiform convulsions. Gastric and intestinal disturbance, vomiting, diarrhea and pain may also occur.

The methyl monohalides are used in the chemical industry for the preparation of various methyl compounds. Methyl chloride is also used as a refrigerant; when employed for this purpose in dwelling houses leaks may have fatal consequences.

The di-, tri-, and tetra- halogen compounds of methyl are virtually nonreactive; their action is exerted by the undecomposed molecule.

Trichloromethane or chloroform was formerly widely used as a surgical anesthetic; but its dangers to the patient outweigh its ease of administration, and it has been largely displaced by ethyl ether. Tetrachloromethane or carbon tetrachloride is extensively employed as a noninflammable grease extracting agent and as a fire extinguishing fluid, for which use it is usually disguised under a trade name, such as "pyrene." The decomposition of chloroform and carbon tetrachloride into phosgene on exposure to heat has been discussed in the section devoted to this irritant. (Chapter IX.)

Both chloroform and carbon tetrachloride exhibit powerful anesthetic properties. In addition their action is depressant to the heart muscle, and disturbing to conduction; so that death from their inhalation may follow failure of the heart or fibrillation of the ventricle rather than failure of respiration. Fibrillation of the ventricles of the heart, one of the most sudden of all forms of death, results particularly from

HALOGEN COMPOUNDS OF METHYL.

Name	Formula	Boiling Point, ° C.	Industrial Use
Methyl chloride	CH_3Cl	—24.0	Preparation of methyl compounds and as refrigerant.
Methyl bromide	CH_3Br	4.5	
Methyl iodide	CH_3I	44.0	
Methylene dichloride	CH_2Cl_2	41.0	
Trichloromethane	$CHCl_3$	61.2	Surgical anesthetic. Grease solvent.
Tetrachloromethane	CCl_4	76.7	Non-inflammable fire extinguishing fluid and grease solvent.

[3] Nicloux, Compt. rend. Soc. Biol., 1906, LX, 144, 245, 373.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF HALOGEN COMPOUNDS OF METHYL.

	Parts per Million Parts of Air	
	Chloroform	Carbon Tetrachloride
Slight symptoms after several hours of exposure [4]	200	1,600
Maximum concentration that can be inhaled for 1 hour without serious disturbance [4]	5,000 to 6,000	4,000 to 6,000
Dangerous after 30 minutes to 1 hour of exposure [4]	14,000	24,000 to 32,000
Rapidly fatal for short exposure [2 and 5]	25,000	48,000 to 63,000

[4] Kobert, R., Kompend. d. prak. Toxikologie, Stuttgart, 1912, 45.
[5] Lehmann, K. B., Arch. f. Hygiene, 1911, LXXIV, 1.
[2] Herrmann, G., Inaugural Dissertation, Würzburg, C. Fuchs, 1911.

light chloroform anesthesia combined with nervous excitement or such drugs as adrenalin. Prolonged exposure leads to degeneration of the liver; occasionally the kidneys and pancreas are also affected. The concentrations of chloroform in the blood causing anesthesia are between 0.2 and 1.5 grams per liter, and those causing death between 0.4 and 1.8 grams.

Halogen Compounds of Ethyl and Higher Hydrocarbons.

The monohalogen compounds of ethyl are decomposed in the body in the same way as with the methyl compounds. The ethyl alcohol formed, however, unlike methyl alcohol, is reactive and is largely destroyed; for it may be oxidized nearly as rapidly as it is formed. The main action of these compounds therefore is exercised prior to their decomposition. These substances are anesthetics, like chloroform, but to a somewhat less degree; they have a depressant action upon the heart muscle, disturb its conductivity, and are prone to induce fibrillation. Full surgical anesthesia can be obtained by the inhalation of ethyl chloride; ethyl bromide has also been tried as an anesthetic. The action of both is rapid and recovery equally rapid; but neither is as safe as ethyl ether.

The concentrations of ethyl chloride in the blood causing unconsciousness are 0.2 to 1.5 grams per liter and those causing death 0.4 to 1.8 grams.[6] Dichloroethylene and ethylene dichloride are similar in

Halogen Compounds of Ethyl and Ethylene.

Name	Formula	Boiling Point, °C.	Industrial Occurrence
Ethyl chloride	C_2H_5Cl	12.5	Surgical anesthetic and refrigerant.
Ethyl bromide	C_2H_5Br	39.0	
Ethyl iodide	C_2H_5I	72.0	
Dichloroethylene	$C_2H_2Cl_2$	55.0	
Ethylene dichloride	$C_2H_4Cl_2$	85.0	
Trichloroethylene	$CHClCCl_2$	87.0	Grease solvent.
Trichloroethane	$CHCl_2CH_2Cl$	115.0	
Perchloroethylene	C_2Cl_4	119.0	
Tetrachloroethane (Acetylene Tetrachloride)	$CHCl_2.CHCl_2$	147.2	Solvent for cellulose acetate.
Pentachloroethane	CCl_3CHCl_2	161.7	

action to ethyl chloride but are more toxic. A concentration of 44,000 parts of dichloroethylene per million of air (4.4 per cent) is rapidly fatal. Trichloroethane, perchloroethylene, tetra- and pentachloroethane are similar to chloroform in their action. Tetrachloroethane is the most

[6] Cushny, Pharmacology and Therapeutics.

toxic of the halogen derivatives of the hydrocarbons; but pentachloroethane is only slightly less toxic. Both of these compounds are essentially like chloroform in anesthetic action, but have a much more pronounced delayed effect upon the liver, as indicated by the jaundice which develops from slight poisoning, and the acute degeneration of this organ from severe poisoning. The heart and kidneys are also affected.

Tetrachloroethane is used as a solvent for cellulose acetate in aëroplane "dope," in the manufacture of artificial silk and pearls, and in that of noninflammable moving picture films.

Physiological Response to Various Concentrations of Halogen Compounds of Ethyl and Higher Hydrocarbons.

	Parts per Million Parts of Air			
	Trichloroethylene [2, 5]	Perchloroethane [2, 5]	Tetrachloroethane [2, 5]	Pentachloroethane [2, 5]
Rapidly fatal for short exposure	37,000	30,900	7,300	9,600

[2] Herrmann, G., Inaugural dissertation, Würzburg, C. Fuchs, 1911.
[5] Lehmann, K. B., Arch. f. Hygiene, 1911, LXXIV, 1.

Subgroup III. Hydrocarbons, Aromatic Series, Injuring Chiefly the Hematopoietic System.

The hydrocarbons of the benzene series are usually derived from the destructive distillation of coal and are, therefore, by-products of the illuminating gas and coke industries. Crude coal tar is a black viscid liquid of specific gravity 1.1 to 1.2, and is a mixture of many organic substances. The crude tar is used for waterproofing the foundations of buildings, for tarring streets, for impregnating roofing felt and for many other purposes. Poisoning can be produced by inhalation of the vapors given off when the crude tar is heated; these vapors are chiefly the first distillation fractions.

Coal tar, after the watery "gas liquor" has been driven off, is separated into the following fractions, each of which is a mixture of several substances.

Often the distillation is not carried thru to completion. When only the light oils and a considerable part, but not all, of the heavy oils have been distilled off, soft pitch remains; when the light oils and only a small portion of the heavy oils have been removed, the residue is known as asphaltum. The low volatility of the materials in soft pitch and asphaltum renders poisoning from their vapors unlikely at ordinary temperatures.

Distillation Fractions of Coal Tar.

(1) "Light Oil" or crude naphtha collected up to 170° C.	Principal constituents benzene, xylene, toluene, pyridine and thiophene.	Sufficiently volatile under ordinary conditions to cause poisoning from the inhalation of the vapors. This fraction is redistilled into 90 per cent benzene, 50 per cent benzene, and solvent naphtha.
(2) "Middle Oil" collected between 170° and 230° C.	Napthalene and phenol.	Not sufficiently volatile under ordinary conditions to cause poisoning from the inhalation of the vapors.
(3) "Heavy Oil" collected between 230° and 270° C.	Phenol, cresol and anthracene (called creosote).	
(4) "Anthracene Oil" collected above 270° C.	Anthracene, phenanthrene, and hydrocarbons which are solid when cooled.	
(5) Pitch remaining in still		

The "light oil," or first fraction of distillation, is redistilled into fractions coming over respectively between 80° and 110°, 110° and 140°, 140° and 170°C. These fractions consist principally of hydrocarbons, but they also contain basic substances such as pyridine, and acid substances such as phenol, besides other constituents. The basic and acid substances are removed by washing in turn with sulfuric acid and caustic soda, and are subsequently recovered.

The fraction of the "light oil" separated between 80° and 110°C. consists principally of the hydrocarbons benzene and xylene, and is handled commercially as "90 per cent benzene." The fraction obtained between 110° and 140°C. consists essentially of the same two hydrocarbons, but in different proportion, together with xylene, and passes under the trade name of "50 per cent benzene." The last fraction, 140° to 170°, consists of xylene and higher homologues together with unknown hydrocarbons, and is called "solvent naphtha."

The fractions termed "90 and 50 per cent benzene" contain respectively about 70 and 46 per cent of pure benzene; the trade terms refer to the proportion of the mixtures which distills over below a temperature of100°C. Pure benzene is obtained by further purification of "90 per cent benzene." All but the most refined products contain small quantities of toluene, paraffines, and carbon disulfide, as well as other impurities including thiophenes. Thiophenes resemble benzene closely in chemical and physical properties, and can be separated only with difficulty.

The commercial benzenes are used extensively as constituents of

quick drying paint and also as a general paint reducer, as a substitute for turpentine. The use of benzene in paint is dangerous unless there is free ventilation; the benzene evaporates rapidly from the painted surface and contaminates the air. The concentration in the air rises at an even greater rate if the surface painted is warm, as in the case of metal work about machinery, or if a spray pump is used to place the paint. Less dangerous, altho not without risk, is the use of benzene-free solvent naphtha (boiling point 140°C.) as a paint medium. This substance evaporates more slowly than benzene and therefore cannot replace it in quick drying paints.

Benzene is used to a limited extent for the extraction of fats and oils, and as a solvent in rubber cements. The use of benzene in motor fuel is discussed in the sections devoted to petroleum and to carbon monoxide.

In the literature the relative toxicity of benzene, toluene and xylene is uncertain. Some observers believe toluene and xylene to be more toxic than pure benzene, while others arrive at the opposite conclusion. Probably there are no great differences in toxicity. On theoretical considerations the expectation would be that the three homologues would be toxic in the order of their ascent in the series; that is benzene least and xylene most toxic, when the toxicity is compared on the basis of concentration in the blood. The diminishing solubility on ascent in the series would, however, tend to counterbalance the increasing toxicity and thus approximately equalize the toxic concentrations of the vapors of the three substances.

The early effects of various concentrations of benzene, and also of toluene and xylene, and therefore of commercial grades of benzene as well, are given in the following table. These concentrations do not take into consideration the chronic effects of prolonged exposure.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF COAL TAR DISTILLATION PRODUCTS.*

	Parts per Million Parts of Air
	Benzene, Toluene and Xylene
Slight symptoms after several hours of exposure[†]	1,570 to 3,130
Maximum concentration that can be inhaled for 1 hour without serious disturbance[†]	3,130 to 4,700
Rapidly fatal for even short exposure[†]	19,000

* The concentrations given here are for acute effects; exposure of several hours a day to concentrations lower than those mentioned leads in a short time to chronic poisoning.

[†] U. S. Department of Interior, Bureau of Mines, Technical Paper 272, 1921.

It is to be noted that the concentrations given in this table do not differ greatly from those for corresponding effects from gasoline; and in the production of acute symptoms the hydrocarbons of the benzene series are not much more toxic than the petroleum distillates. The symptoms of acute poisoning are also much the same. But the late developing chronic effects are quite unlike; prolonged inhalation of benzene and its homologues, even in small amounts, leads to subacute and chronic poisoning directed particularly against the hematopoietic system, whereas a similar condition does not follow from exposure to petroleum distillates.

Benzene, toluene, and xylene, after being absorbed into the body, are largely eliminated thru the lungs when fresh air is breathed. From 15 to 30 per cent of the benzene absorbed is oxidized in the body to phenol and dioxybenzenes which combine with sulfuric and glycuronic acid and in these combinations are eliminated thru the urine. A small amount of benzene is also broken down into meconic acid. In the case of toluene and xylene the action is centered upon the methyl side chains. Toluene is oxidized to benzoic acid, which is then combined with glycocoll to form hippuric acid and excreted in the urine in that form. Xylene is oxidized on only one side chain and forms toluic acid, which is excreted in combination with glycocoll as toluric acid. The complete elimination of benzene, toluene and xylene is effected slowly; this statement, however, has reference particularly to the oxidation products, for the low solubility of the hydrocarbons in blood results in their rapid elimination thru the lungs. The chronic symptoms of benzene poisoning may arise from the oxidation products, which tend to accumulate on repeated exposure. Xylene and toluene are less active than benzene in causing chronic poisoning.

The effects of chronic benzene poisoning upon the blood are three: a decrease of red blood cells resulting in profound anemia; a diminution of the substances concerned in clotting, resulting in hemorrhages; and a loss of white cells and of the substances concerned in defending the body against bacteria resulting in liability to infection. There is considerable variation in susceptibility to chronic benzene poisoning; young persons of both sexes and particularly pregnant females show the greatest susceptibility.

No definite figures have been established for the concentrations of benzene causing chronic poisoning. Analyses of the air in factories where poisoning has occurred give values ranging from 5,000 down to 200 parts of benzene per million parts of air.

Subgroup IV. Hydrocarbons Injuring Chiefly the Nervous System.

Alcohols.

The alcohols have a high solubility; the first three members of the series are miscible with water in all proportions. In consequence even low concentrations in the air inhaled would result, if equilibrium were reached with the blood, in the development of high concentrations within the body. Their solubility also causes them to be eliminated only slowly through the lungs. The slow elimination is, however, in part counterbalanced by the oxidation of some of the alcohols within the body. This destruction of alcohol in the body is particularly marked for ethyl alcohol; but does not occur to more than a small extent with methyl alcohol. Ethyl alcohol is more toxic than methyl for equal concentrations maintained in the body; but the rapid oxidation of ethyl alcohol to water and carbon dioxide prevents its acting as a serious toxic agent when it is absorbed thru the lungs from any ordinary concentration of its vapor in air.

Some degree of tolerance can be developed to the anesthetic action of the alcohols. This tolerance is most marked with ethyl alcohol; it is probably due to an acceleration in the rate of oxidation, and thus to a more rapid lowering of the concentration in the blood, rather than to any change in the sensitivity of the nervous system.

The alcohols have, in addition to their anesthetic action, some direct poisonous action; and this is particularly marked in the case of methyl alcohol. Butyl, propyl and amyl alcohol have little practical importance as noxious vapors for altho the pharmacological activity rises in ascending the series it is more than offset by the decreasing solubility and volatility.

The comparative lethal amounts of the alcohols as determined by Baer are as follows: [8]

	Relative Toxicity
Methyl alcohol	0.8
Ethyl "	1.0
Propyl "	2.0
Butyl "	3.0
Amyl "	4.0

Methyl alcohol is encountered commercially under a variety of names: methanol, wood alcohol, wood spirits, methyl hydrate, wood naphtha, columbia spirits, and colonial spirits. The term "methanol"

[8] Baer, Arch. de physiol., 1898, 287.

has been generally adopted to avoid confusion with ethyl alcohol. Methanol is the main constituent of shellac and of some lacquers. The pure alcohol is colorless and in taste and odor is similar to ethyl alcohol. Crude methanol contains acetone, ethyl methyl ketone, methyl and dimethyl acetate, purpural, allyl alcohol, and other bodies which give to it a disagreeable odor and taste. There is a common belief, quite without foundation, that the toxicity of methanol is due to the impurities which it contains and that pure methanol is not toxic. Reid Hunt [9] has shown that while the toxicity, when the liquid is taken by mouth, may be slightly increased by the presence of large amounts of impurities, even under these circumstances methanol itself is still the chief toxic agent. The impurities do not contribute appreciably to the toxicity of the vapor; the vapor of pure methanol is an anesthetic, a nonreactive gas of high solubility, which therefore accumulates in the body and exerts a direct poisonous action upon the nervous system, particularly upon the retina.

Impure methanol is used as a denaturant of ethyl alcohol and is added to the extent of about 10 per cent. A few instances of poisoning from the vapor of methanol in this mixture have occurred from its use in the radiators of motor cars as an anti-freezing agent. In these cases the fumes from the heated alcohol in the radiator have escaped into the enclosed cabs of trucks built with the radiator outlet discharging into the cab. Ordinarily, however, poisoning from inhalation of the vapor of methanol occurs as the result of applying shellac or other lacquers and inhaling the vapor in an enclosed space; inside of a wooden vat, for example.

Ethyl alcohol is more toxic than methyl when each is taken in a single very large dose. The factor which gives to methanol its particularly toxic character is the slowness of its elimination, from which result both continuous prolonged action and cumulative effect when the exposure is repeated. Only a small fraction of the methanol absorbed into the body is oxidized; the remainder is eliminated largely thru the expired air. The great solubility of this alcohol renders the elimination thru this channel slow. The coma caused by large doses of methanol may last from two to four days; that of ethyl alcohol seldom as long as 24 hours.

More than a week is required to eliminate the methanol acquired by a single large absorption. If the exposure is repeated before the elimination is completed a cumulative effect results; the amount absorbed at each exposure is added to that which remains uneliminated. A toxic concentration is thus gradually built up in the blood as a result

[9] Hunt, Johns Hopkins Hospital Bulletin, 1902, XIII, 137, 213.

of exposure to concentrations which cause no appreciable effect on a single exposure.

The characteristic poisonous action of methanol is exerted particularly upon the optic nerve; probably commencing in the retina. No reason is known for the election of the retina for the action of methanol; it is, however, not characteristic of methanol alone for similar effects are produced by quinine and salicyl. As a rule the involvement of the eye is first indicated by blurred and clouded vision; then pain in the eyeball; partial or complete blindness follows. After a few days the vision generally improves. Occasionally the improvement is permanent; but more commonly there is a second gradual failure of vision leading to permanent blindness. While the effects upon the eye are particularly striking, the irritative action of methanol is not limited to the retina and optic nerve; for among other symptoms severe colic may follow inhalation of the vapor.

The destructive action of methanol upon nervous tissue has been variously ascribed to formic acid and formaldehyde formed by the oxidation of the alcohol within the body. As neither of these substances can exist in the alkaline media of the body it seems more probable that the action is due to the unoxidized methanol.

The cumulative action of methanol together with the lack of quantitative data concerning its action within the body prevent a statement of its minimal toxic concentration. Loewy and v.d. Heide [10] state that 200 parts per million in the inspired air lead to toxic effects in animals if inhaled for a sufficiently long period.

MONOHYDRIC ALCOHOLS.

Name	Formula	Boiling Point, ° C.	Solubility in Water at 40° C. by Volume	Vapor Pressure at 40° mm.	Physiological Action
Methyl Alcohol.	CH_3OH	66.0	Miscible	259.4	Anesthetic in progressively greater degree.
Ethyl Alcohol..	C_2H_5OH	78.5	"	133.8	
Propyl Alcohol.	C_3H_7OH	97.5	"	53.8	
Butyl Alcohol..	C_4H_9OH	117.0	15.1	31.6	Slight irritant action and variable amount of poisonous action upon protoplasm.
Amyl Alcohol..	$C_5H_{11}OH$	137.0	2.0	10.6	

Higher members of the series are not sufficiently volatile to exert physiological action under ordinary conditions.

Dihydric and polyhydric alcohols are not of toxicological importance in the vapor state.

[10] Loewy and v. d. Heide, Biochem. Zeitschr., 1914, LXV, 230.

The treatment of methanol poisoning in the early stages should be directed to ventilating the substance out of the body through the lungs by inhalation of air or oxygen to which a sufficient amount of carbon dioxide is added to maintain a largely increased respiration.

Carbon Disulfide.

Carbon disulfide (CS_2, boiling point 46°C.) is employed in the rubber industry as a solvent for sulfur chloride.

Acute poisoning by carbon disulfide resembles that by chloroform; the two substances have also approximately the same toxicity. Acute poisoning is, however, rarely seen in industry; chronic poisoning is much more common.

The protoplasmic poisonous action of carbon disulfide is exerted upon the nervous system. In prolonged exposure it induces a polyneuritis which may involve any part of the nervous system. The symptoms of the nerve involvement are, therefore, variable and depend upon the locus of the action and its severity. The chronic poisoning usually commences with general disturbances in sensation, such as headache, vertigo, and paresthesias. If the exposure is continued evidence of the involvement of motor nerves appears, and there are tremors and muscular weakness. The polyneuritis may also occur in sensory nerves and give rise to areas of anesthesia or cause blindness from its extension to the optic nerve. The toxic action is also exerted upon the cortical region and causes changes in the temperament, transient excitement, periods of dullness and apathy, hallucinations, and even acute mania which may be permanent. Mild cases recover after discontinuing exposure to the vapor; but a long time is required. Serious nervous disturbances are usually permanent in some degree.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF CARBON DISULFIDE.*

	Parts of Carbon Disulfide per Million Parts of Air
Slight symptoms after several hours of exposure[7]	322 to 386
Maximum concentration that can be inhaled for 1 hour without serious disturbance[7]	483 to 807
Dangerous after 30 minutes to 1 hour of exposure[7]	1,150

* The concentrations given here are for acute effects; exposure of several hours a day to concentrations lower than those mentioned leads in a short time to chronic poisoning.

[7] U. S. Department of Interior, Bureau of Mines, Technical Paper 272, 1921.

Thiophene.

Thiophene (C_4H_4S) is derived from the distillation of coal tar and accompanies the fraction containing benzene from which it is separated

with difficulty. Commercial benzene contains about 0.5 per cent of thiophene. It resembles benzene in its physical character and boils at 84°C.

Thiophene is less toxic than benzene; 50 parts per million of air are borne by animals for an hour without symptoms of poisoning while a similar concentration of benzene brings on symptoms at once.[11] Nothing is known of its action in prolonged exposure.

For Bibliography see end of Chapter X.

[11] Rambousek, J., Industrial Poisoning, London, 1913, 206.

Chapter XIII.

Group III (continued). Volatile Drugs and Drug-like Substances.

Subgroup V. Organic Nitrogen Compounds, Acting Upon the Blood and Circulation.

The organic nitrogen compounds which are volatile belong to the anesthetic series of hydrocarbons, but their anesthetic properties are obscured. The nitrite, nitroso, and amine radicles which they contain exert a more powerful and entirely different action from that of their carbon radicles. All of these substances have the property of altering the hemoglobin of the blood to methemoglobin. In addition the alkyl compounds induce in a high degree the so-called "nitrite effect," consisting primarily in a general arterial dilatation. Nitrous fumes have a similar action, but are mainly characterized by their irritant effects and are therefore discussed under irritant gases in Chapters VIII and IX. Thus over and above their obscured anesthetic action, the organic nitrogen compounds have in varying degree two additional distinct properties: (1) that of lowering arterial pressure, and (2) that of impairing the oxygen carrying power of the blood.

Alteration of Oxyhemoglobin to Methemoglobin.

Methemoglobin is an isomere of oxyhemoglobin. They have the same chemical composition but their structure is different. Methemoglobin holds the same amount of oxygen as oxyhemoglobin, or according to Nicloux half as much; but the combination is firmer and the oxygen is not dissociated even by a vacuum. The stability of methemoglobin prevents it from performing the normal function of hemoglobin; the transportation of oxygen in the body. For this reason the formation of methemoglobin causes asphyxia of the tissues.

If the formation of methemoglobin is extensive, not only is a large part of the hemoglobin irremediably injured, but the red corpuscles are broken up and their contents diffused in solution in the plasma of the blood. Profound anemia may thus result soon after even a single intense exposure. Some of the methemoglobin passes into the urine and imparts to it a characteristic reddish brown or chocolate color.

The loss of hemoglobin through the kidneys is particularly serious, as it involves a depletion of the body's store of iron, which is necessary for the formation of new hemoglobin and fresh corpuscles.

When the effects are less acute the pigment portion of the hemoglobin only is lost, largely by excretion thru the bile, while most of the iron is retained. After very slight exposure involving no destruction of corpuscles, it is possible that some or all of the hemoglobin may return to its normal form without requiring replacement. But as compared to the completeness of recovery of the corpuscles after exposure to carbon monoxide, the degree of spontaneous and rapid recovery from the effects of the nitro gases is slight. Time is required for the body to replace the hemoglobin and corpuscles which have been injured or destroyed.

The anemia produced by the loss of red cells acts as a stimulus to further cell production by the bone marrow. Chronic exposure to gases causing the formation of methemoglobin leads in this way to a relatively high blood count, but also to a diminished hemoglobin content, a low color index in the blood, and to the appearance of imperfectly formed red cells in the blood stream.

The conversion of oxyhemoglobin to methemoglobin, as a rule, develops some hours after exposure to the gas or vapor. The symptoms depend upon the degree of this conversion and the destruction of red cells. In cases of mild poisoning the urine may be discolored and slight cyanosis may appear without serious symptoms of asphyxia. In more acute poisoning the symptoms of asphyxia are marked. The blood becomes chocolate brown and thicker than normal; anemia then develops. The skin, particularly of the face and lips, is cyanosed. The muscles become weak; collapse and unconsciousness follow. Respiration is increased both in rate and in minute volume, and the pulse is rapid. Convulsions frequently precede death, which finally results from failure of respiration.

Nitrite Effect.

The nitrites have a powerful action on the arteries, causing them to dilate by depressing the tone of the muscle of the arterial walls. This effect is particularly marked in those compounds in which the radicle, —NO, is attached to the other group thru an atom of oxygen as in R—O—NO. The alkyl nitrites, such as ethyl nitrite, C_2H_5—O—NO, show this combination. The closely allied group of nitrates in which the nitrogen has five valences and is attached to the radicle by oxygen, as in R—O—NO_2, does not affect the blood vessels. Some of the nitric esters, however, such as nitroglycerine, are reduced by contact with organic material, and nitrites are formed;

these nitrates therefore produce effects like those of nitrites, but their action is slower. The nitro substitution products in which the nitrogen is attached to the alkyl group directly, and not thru an atom of oxygen, as in $R - NO_2$, have a feeble action upon the blood vessels, due presumably to splitting off the NO_2 in the tissues.

The "nitrite effect" exerts its action directly upon the blood vessels, and dilates them widely. This is not effected thru the centers of the vasomotor nervous system. In consequence of the arterial dilatation the blood pressure falls. Practically all of the immediate symptoms occasioned by the inhalation of nitrites arise from the fall in blood pressure. The heart rate is accelerated, not directly by the action of the nitrite, but as the result of the fall in blood pressure. In large quantities, however, the nitrites extend their action to the heart muscle, and the heart beats are weakened.

The decreased supply of blood to the brain, induced by the lowering of blood pressure, gives rise to headache, weakness, and in severe cases to stupor. It also excites the respiratory center in a manner similar to oxygen want. Breathing is quickened and deepened; but in severe cases it eventually becomes slower, shallower, and finally stops. Death then results from asphyxia.

Treatment of Poisoning by Nitrites.

The "nitrite effect" of substances entering the body thru the respiratory tract usually ceases soon after the inhalation is stopped. The headache and other minor symptoms may, however, persist for some time. They are alleviated to some degree by the increased flow of blood to the head when the patient lies down with his feet raised above the level of the head.

The conversion of oxyhemoglobin to methemoglobin is treated by the inhalation of oxygen, preferably in a chamber in which the oxygen pressure can be raised above atmospheric pressure, and by blood transfusion. The administration of sodium bicarbonate has been suggested, but is of uncertain effectiveness, as a means of arresting or even reversing the conversion of hemoglobin to methemoglobin.

Classification of this Subgroup.

For convenience of description the more important gases and vapors of this subgroup acting upon the blood and circulation may be further divided into two classes as follows:

(a) Substances whose predominant action is the "nitrite effect," but which also convert oxyhemoglobin to methemoglobin to some degree. The especially important substances of this class are: alkyl nitrites and alkyl nitro substitution products.

(b) Substances whose predominant action is the conversion of oxyhemoglobin to methemoglobin, with relatively little "nitrite effect." The important substances of this class are: amido compounds and aromatic nitro substitution products.

Alkyl Nitrites and Nitro Substitution Products. These substances have only a limited industrial occurrence. Ethyl nitrite is present in the fumes arising during the manufacture of fulminate of mercury. Amyl nitrite is used in medicine to induce a fall in blood pressure, particularly in the treatment of angina pectoris. They are all powerful drugs and even in small quantities rapidly induce their characteristic effect. But unless the exposure is protracted the effects pass off quickly after the inhalation ceases. For example, inhalation of the vapors arising from 1 gram of amyl nitrite, held upon a cloth below the nostrils, causes a fall of 10 to 15 mm. in the arterial pressure, reaching its maximum in 3 minutes and returning to normal in 7. Habituation can, to some extent, be acquired to the alkyl nitrites; but the partial immunity disappears within a few days after the exposure ceases, and has to be reacquired.

The nitrite effect induced by the alkyl nitrites is much more marked than their action upon hemoglobin; methemoglobin is formed only after severe or prolonged exposure.

Aromatic Nitro Substitution Products and Amido Compounds. These substances are extensively used in the dye industry and for the manufacture of explosives. Fortunately their boiling point is high and their volatility consequently rather low, so that their action in the vapor state is limited by the relatively low concentration which the air can support even at full saturation at room temperatures. The majority of cases of poisoning by these compounds occurs from their absorption thru the skin or from inhalation of the dust of the higher members of the series which are solid at ordinary temperatures.

As in the case of the anesthetic hydrocarbons, the chemical structure of the nitrogen derivatives of the aromatic series influences the intensity of their action. The attachment of the nitroso group (NO) and the nitro group (NO_2), either on a side chain or on the benzene ring, increases the toxicity of the cyclic hydrocarbons. Thus nitrobenzene is more toxic than benzene. The toxicity, however, does not increase in proportion to the number of NO_2 groups added.

Reduction of the NO_2 group to NH_2 as in changing nitrobenzene to aniline reduces the toxicity. The introduction of an alkyl radicle into the amido group likewise reduces the toxicity; thus the alkyl anilines are less toxic than aniline. The sulphonation of the amido compounds destroys their toxicity. The entrance of the carboxyl radicle (COOH)

brings about a similar change; nitrobenzoic acid is not toxic.

The action of the aromatic nitro-substitution products and amido compounds is primarily upon the blood. By converting oxyhemoglobin to methemoglobin they give rise to the symptoms of anemia. The amido compounds undergo a partial oxidation in the body with the formation of amidophenol or its derivations. Their toxic action is exerted largely thru this substance.

In addition to their action upon the blood the nitro substitution products act to some extent upon the central nervous system, causing first stimulation and then paralysis. With the amido compounds this action is much less. In chronic poisoning the liver may become involved from the excessive destruction of the red cells of the blood; and jaundice results.

AROMATIC NITRO SUBSTITUTION PRODUCTS AND AMIDO COMPOUNDS.

Name	Formula	Boiling Point, ° C.	Approximate Vapor Pressures at 40° C. mm.	Physiological Action
Nitrobenzene	$C_6H_5NO_2$	205	0.5	Chiefly exerted in transformation of hemoglobin to methemoglobin and consequent anemia.
Aniline	$C_6H_5NH_2$	183	1.0	
Toluidine	$C_6H_5CH_3NH_2$	197	0.8	
Ortho and meta		203	0.7	
Methyl aniline	$C_6H_5NHCH_3$	191	0.9	
Dimethylaniline	$C_6H_5N(CH_3)_2$	192	1.0	

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF AROMATIC NITRO-SUBSTITUTION PRODUCTS AND AMIDO COMPOUNDS.

	Parts per Million of Air		
	Nitrobenzene	Aniline	Toluidine
Slight symptoms after several hours exposure	0.2 to 0.4	7.0 to 26.0	6.0 to 23.0
Maximum amount that can be inhaled for one hour without serious disturbance	1.0	105.0 to 160.9	91.0 to 140.0

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Chapter XIV.

Group IV. Inorganic and Organometallic Gases.

The inorganic and organometallic volatile compounds have a wide diversity of action. They are classified together here merely because they do not come under any of the other classes. The elements mercury and phosphorus, and the organometallic compounds are essentially protoplasmic poisons, that is inherently poisonous to all living matter. On the other hand, the hydric compounds, such as hydrogen sulfide, show a diversity of actions which necessitates a separate description for each.

Protoplasmic Poisons.

A protoplasmic poison is one which, even in very small amounts, destroys the vitality of any form of living matter with which it comes in contact. Such poisons are fundamental in their action, and do not depend upon the disruption of some system of functions, such as respiration, circulation, or the nervous system, which the complexity of the body renders necessary for the maintenance of the whole organism. The distinction may be seen by comparing the action of mercury with that of the nitrites. Mercury is a protoplasmic poison, for it stops the metabolism of all living matter; the nitrites, on the other hand, exert a specific action upon the minute muscles of the blood vessels, and thus disturb their function. The dilatation of these vessels lowers the blood pressure; the circulation to the various organs is diminished; and they suffer in consequence. But they are not directly affected by the action of the nitrite.

Most of the substances classed as irritants are protoplasmic poisons in the strict sense, for they destroy any tissue with which they are brought in contact. Their action in most instances, however, prevents their absorption into the body, and thus their effects are limited to surface tissues. Likewise the cyanides are protoplasmic poisons, but their action is so specialized that they are better described under the asphyxiants.

The definition used here for protoplasmic poisons is to a certain extent the same as that applied to the anesthetic hydrocarbons; that is, substances which, after absorption, produce organic changes in the

tissues. The milder effects of the hydrocarbons are, however, completely reversible, while those of the typical protoplasmic poisons even from slight intoxication tend to be of a lasting character. Altho a substance is classed as a protoplasmic or general poison, it does not necessarily follow that its action is exerted equally upon all the tissues of the body. It may indeed affect all tissues when it is present in high concentration, but low concentrations may produce noticeable effects only on a single tissue. Thus the protoplasmic poisons when absorbed into the body may select certain organs as the chief point of their action.

Mercury.

Mercury evaporates even at ordinary temperatures, and thus contaminates the air wherever it is exposed. The concentration reached by the vapor in the air depends upon the temperature, the extent of surface exposed, and the rate of air exchange in ventilation. The vapor pressures of mercury and the weight of mercury per liter of air saturated at each temperature are given in the following table.

Temperature, ° C.	Vapor Pressure of Mercury, mm.	Concentration in Air Saturated with Mercury	
		Mg. per Liter	Parts per Million
20	0.0013	.0152	1.84
30	0.0029	.0339	4.10
40	0.0060	.0700	8.50
60	0.0300	.3500	42.50
100	0.2800	3.2600	396.00
200	18.3000	213.0000	25,800.00
300	246.0000	2,879.0000	348,000.00

There is a wide variation in the values given for the vapor pressure of mercury at temperatures below 100°. Those given here seem to be accepted in most chemical tables. The practical utility of the figures given in the above table is of limited value for the reason that they presuppose complete equilibrium between the mercury vapor in the air and the metal with which it is in contact. Only under quite unusual conditions is this state attained. In still air the heavy vapor tends to collect close to the surface of the exposed metallic mercury and thus inhibits further volatilization. Where the air is moved by ventilation, a greater rate of volatilization is attained, but insufficient time is allowed for the air to reach more than partial saturation with mercury. The values given in the table serve only to indicate the limit of attainable air contamination at the various temperatures. It is apparent that temperature has an important practical bearing, inasmuch as the rapidity

of volatilization and the equilibrium concentration both increase greatly with rise of temperature.

The rate of volatilization of mercury at any temperature, and under otherwise similar conditions, varies proportionally with the surface exposed. This has a practical bearing because of the difference in the behavior of mercury in various states of purity. Clean mercury is readily divided into globules, but these globules coalesce when brought together again. On the other hand, mercury soiled by grease and dust is prone to divide into minute globules, which do not coalesce. For example, in the preparation of blue ointment, which is made by working the metal into a grease base, the separate particles cannot be seen with the unaided eye, and the mass assumes a dull greyish color. An analogous condition occurs when mercury is spilled on the floor of a workshop. Under the feet of the occupants of the room it becomes finely divided, and is forced in minute particles into the rough surfaces of wooden flooring and into cracks. The greater the subdivision the larger is the surface which is presented for volatilization. In this manner a comparatively small amount of mercury in an almost or quite invisible state of subdivision may present an exposed surface equivalent to that of a large mass of mercury coalesced in a dish or pan. The vapor has neither taste nor odor to give warning of its presence.

Occupations Liable to Mercury Poisoning. Many occupations, besides those of mining, smelting, and refining, involve the use of metallic mercury. Mercury is employed in the manufacture of thermometers, barometers, heat regulating devices, gas analysers and a large number of other forms of scientific and domestic apparatus. Mercury is used in vacuum pumps employed for extracting air from incandescent bulbs, x-ray tubes, and other apparatus. It is also employed extensively as a conducting or displacement medium in electrical and chemical laboratories. Mercury vapor may escape into the air during the use of an induction furnace. The mercury turbines now being introduced in power plants would be effective in causing poisoning if they leaked.

An extraordinary example of wholesale poisoning by the vapor from metallic mercury occurred in the year 1810 in the British sloop Triumph. This vessel attempted to salvage the mercury from a wrecked Spanish ship which was loaded with this metal. After transfer to the British vessel the mercury leaked into the hold and so into the bilges of the ship and the crew were poisoned by its vapor; 200 sailors were severely poisoned and 3 died.[1]

Even more extensive poisoning occurred in 1804 during a fire in a quicksilver mine at Idria, Austria. Nine hundred inhabitants in the

[1] Phil. Trans. Roy. Soc., 1823, p. 113.

neighborhood developed mercurial tremor; cows and other domestic animals also showed symptoms.[2]

Toxic Concentrations of Mercury Vapor. Göthlin[3] states that the inhalation of 0.4 to 1.0 milligram of mercury vapor daily causes poisoning after some months. Mercury poisoning results after two or three months from the inhalation of air containing 0.0007 milligram of mercury per liter, when the exposure is three to five hours daily. The total daily absorption under these circumstances was estimated as between 0.771 and 1.285 milligrams.

Absorption of Mercury Vapor. Cole, Gericke and Sullivan[4] state that mercury vapor is not absorbed thru the lungs, but only thru the mucous membrane of the upper respiratory tract. They were working on the therapy of syphilis, and were concerned with absorption of the fumes heated to a temperature higher than that of the body and inhaled directly. Under these circumstances the mercury condensed from the heated air on being cooled in the respiratory tract, and was deposited in the mouth and pharynx. Mercury vapor in air inhaled at the temperature of the body or lower does not condense in this way. Because of its low solubility in water the vapor probably passes for the most part to the lungs to be absorbed there.

The mode of absorption from the lungs is unknown. It has been suggested that the mercury brought to the lungs as vapor is deposited as the metal, and is then oxidized. It is more reasonable to suppose that the vapor dissolves in the fluid on the moist surfaces, and thus passes into the blood. Altho its solution is extremely dilute, it probably follows the laws governing the solution of gaseous substances in liquids. The rate at which it passes from the air into the blood is therefore dependent upon the concentration in the air in relation to that in the fluid. When mercury in solution is brought in contact with protein, it forms an albuminate which is soluble in a fluid containing an excess of unaffected protein. The mercury dissolved in the fluids in the lungs is thus constantly removed thru combination with the proteins. In consequence of this removal a continuous passage of mercury from the air into the fluid is effected, and a thoro and rapid absorption of the mercury from the air results. This conception is supported by the observation of Göthlin, that when the concentration of mercury vapor in the air does not exceed 0.00025 milligram per liter it is practically all absorbed.

Excretion of Mercury. The excretion of mercury takes place thru both the urine and feces, and in approximately equal amounts.

[2] Herrmann, Wien. med. Wochenschr., 1850, No. 40.
[3] Göthlin, Hyg. Rundschau, 1911, XXI, 390.
[4] Cole, Gericke and Sullivan, Arch. of Dermat. & Syph., 1922, V, 18.

A small amount of mercury appears also in the saliva and sweat, as well as in the bile and in the gastric and intestinal juices. The excretion begins within a few hours, and after a single dose lasts from one to two weeks; after long continued administration the excretion continues intermittently for many months. The tardiness of complete elimination appears to be due to the formation of deposits in various organs, especially the kidneys and liver. In these organs the mercury appears to be quite firmly bound, forming deposits from which traces of the metal may be mobilized long after the administration is discontinued.

Symptoms of Chronic Poisoning. The main symptoms of chronic mercurial poisoning are salivation, stomatitis, nervous disturbances, and in severe cases nutritional disorders. The subject complains of pain in chewing at a time when all other objective symptoms, except increased salivary secretion, are absent. The gums loosen from the teeth, become red and swollen, and bleed easily. A thin pussy exudate may flow from under the reddened part of the gum. The entire mucous membrane of the mouth becomes involved and turns a peculiar copper color. On the surface of the cheeks and lips sharply defined yellow ulcers develop. The stomatitis is associated with swollen lymph and salivary glands. In severe cases the buccal inflammation may result in the teeth loosening and falling out, in necrosis of the jaw, and in the consequent undermining of the general health. Mercurial stomatitis is usually associated with minor digestive disturbances, such as loss of appetite and diarrhea.

The most striking symptom of chronic mercury poisoning is the psychic disturbance "Erethismus mercuralis." This consists in a peculiar form of excitement and timidity. In severe cases the subject develops a high degree of self-consciousness and embarrassment, so that in the presence of strangers he is unable either to speak or act normally. The disposition is changed so that the subject becomes excitable and nervous; there is sleeplessness, or unpleasant dreams and headache. In mild cases the psychic changes are less marked and the subject complains merely of lassitude, fatigue, and nervousness.

A further involvement of the nervous system is evident in the development of mercurial tremor. This begins with a slight twitching of the face and a more distinct trembling of the fingers. As the poisoning increases the trembling increases in intensity and finally extends to all parts of the body. With the progress of the condition the subject loses more and more the control of his muscles, and the tremor presents a distinct intentional character; thus it appears in greatly accentuated form when he tries to perform some act, such as that of lifting a glass of water to his mouth. When at complete rest the subject does not tremble. He can perform heavy rough work, but he is unable to

perform delicate work requiring finer muscular movements. Since the tremor is initiated by movement, it becomes difficult in very severe cases for the subject to walk unaided. Ataxia is, however, never due to this cause. Pain in the joints and extremities is common in chronic mercurial poisoning; paralysis and peripheral neuritis also occur in rare cases.

The stomatitis, erethism and tremor characteristic of chronic mercurial poisoning are not always, nor usually, present simultaneously in all cases, nor to the same degree. Stomatitis is particularly evident in those cases in which the mercury has been absorbed over a comparatively short period; the same is true of the erethism. Tremor may occur without either of the other symptoms in cases in which the absorption has occurred very slowly over a long period of time. In these cases the other symptoms readily develop from increase in the severity of exposure. The first symptom of erethism is an increase in the tremor when the patient is under observation.

Death rarely results directly from chronic mercury poisoning, but rather from intercurrent disease. Those who are chronically poisoned by mercury are prone to develop tuberculosis. This development probably consists in the recrudescence of existing lesions and the acceleration of the course of the disease. Altho mercury has been suggested for use in the therapeutics of tuberculosis, as has nearly everything else, it has been definitely shown to have a detrimental instead of a beneficial effect.[5]

Treatment and Prevention. The treatment of chronic mercurial poisoning consists in terminating the exposure and in general hygienic and tonic measures. It is very doubtful whether medicinal treatment materially influences the course of the disease. Potassium iodide and baths are customarily tried with the intention of hastening the elimination; but they are of doubtful benefit.

Prophylaxis against poisoning with mercury vapor consists in limiting the area of mercury exposed to the air. Much can be accomplished along these lines by careful handling of the substance and particularly by avoiding the spilling of it upon the floors of workrooms. Raised edges around all sides of the tables or benches upon which mercury is handled, prevent the mercury from being scattered about in a fine state of division. The floors should be made of smooth impervious material free from cracks, and should slope slightly to a collecting trough and basin. Wooden or cement floors should not be permitted. All vessels containing mercury should be kept covered as much as possible.. The ventilation should also be very thoro in rooms where mercury is exposed; and particular attention should be

[5] Hortz, H. J., Journ. Amer. Med. Assn., 1910, LV, 915.

paid to maintaining a low general temperature to limit the volatilization of the metal.

Where exposure to mercury is unavoidable, the dental and oral hygiene of the workers should be closely supervised and enforced. The teeth should be brushed twice daily, and a mouth wash of hydrogen peroxide or potassium chlorate should be used. The teeth should be examined at regular intervals and all carious teeth removed or repaired. There should also be a general medical examination at least every six months. Persons suffering from tuberculosis, or those who have had it, should be excluded from any employment involving the constant or extensive use of mercury. It is advisable to exclude also those with poor kidney function or pyorrhea alveolaris. Women of child bearing age and young persons of both sexes should also be excluded, as they are particularly susceptible to mercury poisoning.

Phosphorus.

White phosphorus volatilizes slowly at room temperature. The vapor given off is partially oxidized in the air so that the fumes consist largely of phosphoric and phosphorous oxide, together with some phosphorus. Of these three the phosphorus alone appears to be toxic. There is a great difference in solubility between phosphorus and its oxides. The element itself is only slightly soluble and is probably absorbed largely thru the lungs; the oxides which readily react with water are taken out of the air by the moisture in the mouth and upper respiratory passages, and are there converted into phosphoric and phosphorous acid.

Toxicology. When elemental phosphorus is absorbed it is believed to be carried in the blood unchanged. Phosphorus in small quantities absorbed daily over a long period exerts a destructive action upon the bones. Different authors present widely different views of the fundamental nature of this action. It appears to be essentially a disturbance in the nutrition of the bones which renders them more than normally fragile; and even more important, it greatly diminishes the resistance of the bones to infection by the tubercle bacillus and other organisms which induce necrosis.

Cases of so-called "spontaneous" fracture are in reality the result of the fragility of the long bones and occur in persons who have undergone prolonged poisoning by the fumes of white phosphorus. The lesion which especially characterizes phosphorus poisoning is necrosis of the jawbone, the so-called "phossy jaw." This necrosis and the accompanying conditions result from infection of the jawbone with organisms from the mouth. The entrance of bacteria is usually effected through a carious tooth or an injury in the gum. Phosphorus does not

directly cause necrosis of the bone, but it lowers its resistance to infection and prevents its healing. The necrosis in some instances extends to the complete destruction of both jawbones. The particular election of the jawbones for necrosis is not due to a special selective affinity of phosphorus for these structures, but to the fact that these bones more than any others are exposed to microörganisms.

As phosphorus vapor has but one action in the body, that of lowering the vitality of the bones, both the necrotic and cachexial symptoms, which may accompany the weakening of the bones, are due to infection. The absorption of material from the necrotic and abscessed areas in the jaw is detrimental to the general health. Death in chronic phosphorus poisoning results from the spread of this infection. Among those seriously affected the mortality ranges between 15 and 20 per cent. The altered nutrition of the bones is apparently a change which persists for a long time. Cases have been reported in which the jawbone became infected and necrosis developed several years after the exposure to phosphorus had been discontinued. More often, after the patient is removed from phosphorus fumes, the necrosis ceases and in time heals, altho often with great disfigurement to the face.

The symptoms of phosphorus poisoning usually commence with a toothache arising from an abscess at the root of a tooth. The wound left by extraction heals incompletely. Suppuration develops, followed by abscess formation, offensive breath, discharge of pus from fistulas and gradual destruction of the bone.

Occurrence of Phosphorus Poisoning. Only a small proportion of the individuals exposed to the fumes of white phosphorus develop "phossy jaw." The number of cases of poisoning and death which results is small in comparison with many other poisons common in industry, such as lead or carbon monoxide. Nevertheless the intense suffering, prolonged course, and great disfiguration of phosphorus poisoning created a strong popular feeling against it. In consequence Finland abolished the use of white phosphorus in the manufacture of matches in 1872, and by 1906 practically all European countries had forbidden the manufacture or importation of white phosphorus matches. In 1909 the United States imposed a tax on these matches which resulted in their manufacture from the harmless sesquisulphide of phosphorus. As a result of this legislation poisoning from the fumes of white phosphorus has been largely eliminated. A few cases still occur in plants producing white phosphorus or in the conversion of the white to the comparatively harmless red phosphorus. The manufacture of phosphorbronze is attended with some danger from phosphorus poisoning.

The treatment of phosphorus poisoning consists in terminating the patient's exposure to the fumes and in surgical treatment of the necrotic bone and abscesses.

Organometallic Compounds.

The toxicology of the volatile organometallic compounds has been little studied. As a rule their action depends upon that of the metal with which the organic group is combined; but their effects are usually far more acute than those of any other compounds of the metals. Their volatility results in their absorption from the lungs, and thus renders the poisoning much more rapid than that ordinarily occurring when salts of the heavy metals are taken in thru the alimentary tract. Ethyl arsine and cacodyl, for example, when inhaled in high concentration produce arsenical poisoning so acutely that death rapidly results. Acute poisoning with lead tetraethyl is especially characterized by maniacal symptoms, which are rarely seen in the ordinary form of lead poisoning; the rapidity of absorption from the lungs in contrast to the alimentary tract, and the almost direct transportation of the lead so absorbed in the blood to the brain explains the difference in symptoms.

Diethyl mercury, on the other hand, is retained in the body, and is only slowly decomposed; so that fatal poisoning may occur altho the symptoms may not have developed for two months or more after the initial absorption.

Chronic poisonings by the organometallic compounds are essentially similar to those induced by the corresponding heavy metals. Only those substances in this class which occur with some frequency need be discussed here.

ORGANOMETALLIC COMPOUNDS.

Name	Formula	Boiling Point, °C.
Diethyl arsine	$(C_2H_5)_4As_2$	190.0
Cacodyl	$[(CH_3)_2As]_2$	170.0
Cacodyl oxide	$[(CH_3)_2As]_2O$	12.0
Diethyl mercury	$(C_2H_5)_2Hg$	159.0
Tetraethyl lead	$(C_2H_5)_4Pb$	....
Nickel carbonyl	$Ni(CO)_4$	....

Diethylarsine. Diethylarsine is said to arise from the action of the mold, penicillium brevicaule, growing upon wall paper printed with arsenical colors. The effects of this compound usually appear as a mild chronic form of arsenical poisoning marked by vague disturbances of nutrition. One acute, but not fatal, case has been reported

in which the symptoms appeared nine hours after the exposure and were largely gastro-intestinal.[6]

Tetraethyl Lead. Tetraethyl lead has been recently introduced, and is now widely used in America, as an antidetonant for internal combustion engines. It is mixed with gasoline to the extent of about 0.1 per cent by weight. The danger of poisoning occurs particularly during the manufacture of the compound, from which several deaths have already occurred, and in the process of blending it with gasoline. Poisoning may occur to a less extent among those handling "ethyl gas," as the mixture is called. Not only are the vapors of lead tetraethyl absorbed thru the lungs, but when the liquid is brought in contact with the skin absorption occurs thru that channel also.

The acute poisoning takes a violently maniacal form; unless restrained the patients commit suicide; if restrained they usually die with acute cerebral symptoms. Treatment should aim to remove the lead from the blood as quickly as possible by immobilizing it in the bones. From the investigations of Aub, Fairhall, Minot and Reznikoff,[6a] it appears that a liberal supply of calcium administered in the form of milk with calcium lactate and some sodium bicarbonate, tends to have this effect.

Chronic poisoning by tetraethyl lead resembles the ordinary chronic form of lead poisoning, which is characterized by nutritional disturbances, paralysis of motor nerves, and increased susceptibility to such diseases as tuberculosis and pyorrhea alveolaris. Lead tetraethyl is destroyed by the combustion in the cylinders of the engine in which it is used; the exhaust gas contains lead oxide and bromide in the form of a fine dust. Ordinary lead poisoning can arise from inhalation of this dust; but according to the report of a commission appointed to study the matter the risk is slight. Whether this view is correct, the future will tell.

Nickel Carbonyl. Nickel carbonyl is formed during the purification of nickel by the Mond Process. A current of carbon monoxide is passed over finely divided nickel; the nickel carbonyl thus formed is then decomposed by heat and the nickel liberated. When inhaled, nickel carbonyl causes irritation of the lungs leading in some cases to edema or pneumonia. Beside this local action there are in some cases disturbances of the central nervous system, such as convulsions and delirium. The amount of carbon monoxide liberated in the body by the decomposition of the carbonyl is too small to play more than an insignificant part in the poisoning. Slight symptoms such as dyspnea and giddiness develop when a high concentration of nickel carbonyl is

[6] Kunz-Krause, Vierteljahreschr. f. gerichtl. Med., 1921, LXI, 16.
[6a] Lead Poisoning, Medicine Monographs VII, Baltimore, 1926.

inhaled; the symptoms pass off on removal to fresh air. After 12 to 36 hours the signs of lung irritation appear, as in the case of other slightly soluble irritants, such as phosgene. In fatal cases death occurs from the fourth to the eleventh day after the exposure.

An atmosphere containing as much as 1000 parts of nickel carbonyl per million parts of air is dangerous to breathe.[7]

Inorganic Hydric Compounds.

The hydric compounds of arsenic, phosphorus and sulfur have a poisonous action entirely different from that of their inorganic element. All of these compounds are highly toxic.

Inorganic Hydric Compounds.

Name	Formula	Boiling Point, ° C.	Physiological Action
Hydrogen Arsenide	H_3As	— 55.0	Destroys red blood corpuscles.
Hydrogen Phosphide, or Phosphene	H_3P	— 85.0	Action uncertain; symptoms from gastro-intestinal tract.
Hydrogen Sulphide	H_2S	— 61.8	Irritant; when absorbed stimulates and paralyzes central nervous system.

Hydrogen Arsenide. Hydrogen arsenide, or arsine, is formed whenever nascent hydrogen is produced in the presence of a soluble compound of arsenic. The lead, zinc, copper, and antimony used commercially often contain arsenic, as also does iron obtained from pyrites. Commercial sulfuric acid made by the chamber process is likewise often contaminated with arsenic, and if this variety of acid is used to make hydrochloric acid the latter also becomes contaminated. Arsine is liberated when an acid acts upon a metal if either contains arsenic. Such conditions are common in industry. The poisoning which sometimes results is often mistakenly attributed to acid fumes. Poisoning by arsine occurs in the manufacture and use of hydrogen for filling balloons when the gas is made from metallic zinc and hydrochloric acid. It occurs also in men who are engaged in charging electric storage batteries; for instance, the entire crew of a submarine is sometimes affected.

Toxicology. The specific action of arsine arises from its affinity for the hemoglobin of the blood corpuscles. On entering the blood

[7] Armit, H. W., Jour. Hygiene, 1908, VIII, 565.

stream arsine is taken up by the hemoglobin forming a compound with this substance. The arsenic in the combination is gradually oxidized to arsenic oxide. Hemolysis occurs at the time of this formation of arsenic oxide within the corpuscles.

The symptoms of acute arsine poisoning result from the hemolysis of the red blood cells, and arise mainly during the excretion of the hemoglobin from the disintegrated corpuscles. The anemia resulting from the loss of red cells also contributes to the symptoms.

Hemoglobin, methemoglobin, hematin, and occasionally blood itself are passed in the urine. Sometimes, however, the urine is suppressed owing to the tubules being plugged with the débris of the corpuscles. Jaundice develops from the formation of an excess of bile pigment from the liberated hemoglobin. The anemia develops in a few hours and in severe cases is extreme; the red cells may fall below a million per cubic millimeter of blood. Many of the fatal cases show edema of the lungs, but it is uncertain whether this condition results from a primary irritation or is secondary to failure of the circulation. The symptoms of acute poisoning usually develop a few hours after the exposure to the gas. They begin as an indefinite feeling of illness and weakness followed by vertigo and faintness. Intense headache develops and is followed by nausea and vomiting with epigastric pain. In severe cases the vomiting becomes continuous and the vomitus contains bloody material. Jaundice develops to a degree depending upon the severity of the poisoning. Cyanosis may also appear. Death from acute arsine poisoning occurs in from 2 to 6 days. The mortality of the recognized cases of arsine poisoning reported in the literature is approximately 30 per cent. Among those surviving these acute effects,

Physiological Response to Various Concentrations of Arsine.

	Parts of Arsine per Million Parts of Air
Slight symptoms after several hours of exposure[8]	30
Dangerous for exposure of 1 hour[8]	50
Fatal to man in exposure of 30 minutes[9]	250

[8] Dubitsky. Quoted from Koelsch. I. Zentralbl. f. Gewerbehyg., 1920, VIII, 121.

[9] Kohn Abrest, E., Annales des Falsifications, 1915, VIII, p. 215.

[10] U. S. Dept. of Interior, Bureau of Mines, Technical Paper No. 248, 1921, p. 67.

symptoms more closely resembling those from ingestion of arsenous oxide may develop. The kidneys are particularly affected, and death may follow.

Chronic or subacute poisoning by arsine has been observed. In this condition both hemoglobin and albumen may appear in the urine and the skin show some yellowness. The subjective symptoms are vague. The diagnosis is made by the presence of arsenic in the urine. The arsenic oxide found in the corpuscles and liberated by their destruction may possibly play a part in chronic poisoning by arsine in addition to the hemolytic activity of the gas.

Hydrogen Phosphide. Hydrogen phosphide, or phosphene, is evolved when water acts upon calcium phosphide. The latter substance is sometimes used to charge marine buoys which by the flare of the spontaneously inflammable phosphene indicate their position on the water. Aside from this use phosphene is not generated intentionally in industrial procedures. Calcium phosphide, however, is frequently a contaminant of calcium carbide and appears in the acetylene generated by contact with water (see acetylene for concentration). Ferro-silicon also contains the phosphide as an impurity and phosphene is evolved when the alloy is moistened. In most of the cases of phosphene poisoning recorded in the literature the gas has been evolved from this source.

The toxicology of acute poisoning by phosphene has not been fully worked out. It does not alter the blood and its effects are apparently exerted largely through the central nervous system. Some inflammation of the lungs results from its absorption; beyond this no changes in the body are demonstrable.

The acute action of phosphene does not resemble that of phosphorus. Instead there is marked dyspnea, purgation, weakness, tremors and finally violent convulsions and death. The symptoms in many ways resemble those resulting from food poisoning and have been mistaken for them. Slight cases recover without after effects.

Prolonged exposure to small amounts of phosphene is said to give rise to chronic symptoms identical with those of phosphorus poisoning.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF HYDROGEN PHOSPHIDE.

	Parts of Hydrogen Phosphide per Million Parts of Air
Maximum amount that can be inhaled for 1 hour without serious result [11]	100 to 200
Dangerous in 30 minutes to 1 hour [11]	400 to 600
Rapidly fatal [12]	2,000

[11] Kobert, R., Kompend. d. prak. Toxikologie, Stuttgart, 1912, 45.
[12] Rambousek, Industrial Poisoning, London, 1913, 191.

Hydrogen Sulfide. Hydrogen sulfide is frequently evolved from the decomposition of organic material; if the material is held in con-

tainers which prevent the rapid escape of the gas, poisonous concentrations are built up. Poisonings from this cause occur in tanneries, fat rendering plants, glue factories and in sewers. Taylor [13] gives the concentration of hydrogen sulfide in the sewer gas of Paris as 2.99 per cent (1897).

Hydrogen sulfide is liberated in the course of chemical reactions during the manufacture of chemicals such as dyes, sulfur monochloride, and barium carbonate made from the sulfide. The gas may also be present in the air of mines and is produced by the decomposition of pyrites. It is also met with in the distillation of petroleum oil containing sulfur, in the handling of certain slags, and in the gas and coal industries. In these latter industries the hydrogen sulfide is encountered in cleaning out the iron oxide beds used for purification of the gas.

Toxicology. Hydrogen sulfide is primarily an irritant gas; the systemic action which in acute poisoning overshadows the irritant action results from the absorption of the products arising from the neutralization of the sulfide by the surface tissues of the respiratory tract. Hydrogen sulfide is discussed as an irritant gas in Chapters VIII and IX.

When hydrogen sulfide is brought in contact with moist tissue, it combines with the alkali present with the formation of sodium sulfide. Irritation is produced both by the abstraction of alkali from the cells and by the sulfide which is caustic. Part of the alkali sulfide is absorbed thru the membranes of the respiratory tract and enters the blood stream. It is there hydrolized with the liberation of hydrogen sulfide. In the presence of oxygen the hydrogen sulfide is rapidly oxidized to the harmless sulfate. The systemic action of hydrogen sulfide is occasioned by the unoxidized hydrogen sulfide held in the blood.

Hydrogen sulfide is generally credited with forming a combination with the hemoglobin of the blood and inducing asphyxia from this cause. In fact, however, it does not combine with oxyhemoglobin, but only with methemoglobin. Since this substance is not normally present in the blood, no sulfur compound is formed with the hemoglobin as a result of inhalation of the gas. On the other hand, sulfomethemoglobin appears in the blood of cadavers and gives a bluish green color to the vessels about the intestines. The sulfomethemoglobin then formed results from post mortem changes involving the formation of methemoglobin, and its subsequent combination with the hydrogen sulfide liberated by the decomposition of the material in the intestines.

Sulfur compounds of hemoglobin are occasionally seen in the blood

[13] Taylor, Medical Jurisprudence, 12 Edt. 1897, 486.

of persons who are not exposed to hydrogen sulfide; in fact sulfomethemoglobinaemia is classed among the enterogenous cyanoses. Its occurrence under these circumstances results from the formation of methemoglobin in the blood and the subsequent union of this pigment with small amounts of hydrogen sulfide arising in the digestive tract. The methemoglobin is formed by the absorption of the products arising presumably from the action of nitroso bacilli living upon the surface of the pharyngeal cavities. (See organic nitro compounds and methemoglobin formation, Chapter XIII.)

Free hydrogen sulfide in the blood acts upon nervous tissue thruout the body and occasions systemic poisoning. In small amounts the sulfide depresses the nervous system; in larger amounts it stimulates, and in very large amounts it paralyzes the nervous system. Bradycardia, convulsions, respiratory stimulation, and paralysis all appear as results of this action of hydrogen sulfide upon the nervous system.

Death in acute hydrogen sulfide poisoning results from failure of respiration and the consequent asphyxia. This respiratory failure is occasioned thru two separate processes depending upon the concentration of the gas inhaled. Concentrations higher than 2,000 parts per million cause almost immediate cessation of breathing by paralyzing the respiratory center. Concentrations between 600 and 2,000 parts per million cause hyperpnea thru stimulation of the respiratory center.[14] The excessive breathing lowers the carbon dioxide content of the blood, and apnea vera results. Spontaneous breathing does not return after the paralytic form of failure, unless artificial respiration is used. After the overstimulated form of failure, breathing may return spontaneously, but it is hastened by the use of artificial respiration and inhalation of oxygen and 5 per cent carbon dioxide.

The action of hydrogen sulfide upon the nervous system is exerted only during the time the free hydrogen sulfide is in the blood and to a degree depending upon the concentration present. The symptoms of acute poisoning develop immediately on the inhalation of the gas; but because of its rapid oxidation in the blood they pass off when the inhalation ceases. Death in acute poisoning is as rapid as in poisoning by cyanides; a man inhaling a high concentration drops dead. Hydrogen sulfide is in a high degree a noncumulative poison; thus if the victim is revived there are no systemic sequelae. In less severe poisoning, convulsions and dyspnea are marked symptoms. In subacute or chronic poisoning the main symptoms are those of irritation, particularly of the eyes, and to a less degree of the respiratory tract. In some cases

[14] Haggard, H. W., J. Pharm. & Exp. Therap., 1922, XIX, p. 262, and Journal of Industrial Hygiene, 1925, VII, p. 113; also Henderson, Haggard and Charlton, Amer. J. Physiol., 1922, LXI, p. 289.

the depressing action of the gas is also evidenced in a mild degree of malaise. The limit of danger for prolonged exposure is said to be a concentration of 50 parts per million or possibly lower.

The treatment of acute hydrogen sulfide poisoning consists in restoring breathing by means of manual artificial respiration, combined with inhalation of oxygen mixed with 5 per cent of carbon dioxide.

PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS OF HYDROGEN SULPHIDE.

	Parts of Hydrogen Sulphide per Million Parts of Air
Slight symptoms after several hours [11]	100 to 150
Maximum amount that can be inhaled for 1 hour without serious disturbance [11]	200 to 300
Dangerous in 30 minutes to 1 hour [11]	500 to 700
Rapidly fatal [11 and 15]	1000 to 3000

[11] Kobert, R., Kompend. d. prak. Toxikol., Stuttgart, 1912.
[15] Sayres, R. R., U. S. Bureau of Mines, Report on Hydrogen Sulfide as an Industrial Poison, Investigations Serial Number 2491, June, 1923.

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Chapter XV.

Prevention and Treatment of Poisoning by Noxious Gases.

In order to prevent poisoning by noxious gases three requirements are essential: (1) The conditions under which each gas occurs must be known, and also the physiological effects induced by various concentrations and by various durations of exposure. (2) This knowledge must be applied so as to prevent the dissemination in the respired air of a toxic concentration of the gas. And (3) if the dissemination cannot be avoided, those who are exposed must be equipped with apparatus to protect them against inhalation of the gas.

Lack of Legal Protection Against Noxious Gases.

At the present time there is an almost complete lack of Federal or State laws applying specifically to the manufacture, handling and sale of substances which are poisonous, other than foods and drugs. This lack of legal protection is the more striking when it is compared with the full and explicit regulations, inspection and analysis applying to the shipment and sale of food products. The public is thus effectively protected against food poisoning, and indeed even against materials which are only mildly detrimental, if they are to be taken into the body thru the alimentary tract. On the other hand, the injury to the public health induced by detrimental materials, even the most poisonous, which enter the body thru the respiratory tract, is not generally recognized; and relatively little protection against such hazards is afforded by legislation. For example, the addition of benzoate of soda or artificial coloring matter to a food product must be indicated by a proper label on the container; but the presence of benzene in a quick drying plant, of carbon disulfide or tetrachloroethane in a solvent, is often disguised under a trade name. Yet benzoate of soda in food can at most only impair health slightly, while benzene in paint causes the death of men who use it in a confined space for a few hours. A dangerous organometallic compound, lead tetraethyl, is now blended with gasoline and is sold thruout this country; it is noteworthy that some other countries are prohibiting the use even of lead paints. The public does not know the dangers of benzene nor the insidious

nature of lead poisoning. In respect to the volatile poisons, and indeed to all harmful substances in industry and in interstate trade, it is of the highest importance that the same sort of inspection and regulation should apply as in the matter of food products under the Pure Food Law. The Federal and State Governments should also provide for more extensive scientific investigation and publication for the education of manufacturers and workmen. Public funds expended for this purpose would bring an ample return; for industry would not then be hampered by the illness of workmen or loaded with the cost of their deaths. With knowledge and care even the most poisonous substance can be produced and used safely in industry. The sale of such substances to the general public is, however, fraught with great danger.

New compounds of volatile nature are being introduced into manufacture and trade in increasing number and amount. Physiological investigation to define the dangers attending the use of these substances should be a matter of course prior to their introduction; it should be a legal requirement and strictly enforced. In fact, however, the toxicity of these compounds is generally unknown at the time of their introduction. Physiological information based largely upon experiments on animals would be both less costly and more humane than is the information now gained on men by the statistics of illness, disablement and death in industry.

Prevention of Atmospheric Contamination.

In order to prevent the dissemination of noxious gases in toxic concentration, the physical and chemical characteristics of the substances, and also their physiological action and degree of toxicity must be known. The mode of preventing a poisonous or unhealthful condition of the air resolves itself then into the engineering problem of controlling the degree of contamination. The requisite standards of ventilation must first be determined experimentally and defined in practical terms, and then arrangements and machinery to effect them must be developed. An example of this type of problem on a large scale occurred in preparation for the construction of the vehicular tunnels under the Hudson River. The first step was to determine the allowable concentration of carbon monoxide from motor exhaust in air to be breathed during the time of passage thru the tunnel; the second was the development of a method and means of ventilation to maintain the standard thus defined. (See bibliography, page 112.)

When factories, petroleum refineries, garbage, fertilizer, and similar plants produce harmful fumes or offensive odors, it is generally possible to prevent the escape of these gases and vapors by one or other of two methods. For both methods it is essential to collect in a single

large duct the entire effluent air from the chambers where the fumes arise. One of the methods [1] then consists in passing this air thru activated charcoal which readily condenses a wide range of substances. Commercially valuable substances absorbed by charcoal may be recovered by displacement with steam, and the absorptive power of the charcoal is thus regenerated. The other process [2] consists in mixing a relatively small amount of chlorine gas with the air in the duct. Minute amounts of chlorine in the presence of water vapor destroy many labile substances including most offensive odors, hydrogen sulfide, etc. It is essential that the volume of chlorine shall be accurately adjusted to the amount of odoriferous substance. For this purpose the same apparatus is applied as that used for chlorinating city water supplies.

Other Precautionary Measures.

No matter how much care is taken to prevent constant contamination of the air, accidental and temporary contamination must also be anticipated and provision must be made for such accidents. The general type of precaution needed may be exemplified by the following rules applicable to an ammonia refrigerating plant:

(1) The refrigerating equipment, including valves and piping, should be inspected at short and regular intervals, and suitable repairs made immediately when needed.

(2) Every employee should be instructed regarding the dangers from ammonia and trained to avoid them.

(3) No one should be allowed to sleep in rooms adjoining the refrigerating plant.

(4) The room or rooms in which the machinery is installed should have doors opening directly to the outside air. The relation of this room to other parts of the building should be such that escaping fumes cannot invade the other parts or cut off the escape of persons in them. Regulations should be prominently posted and strictly enforced requiring that the exits shall never, even for a few minutes, be obstructed by temporary scaffolding, wheelbarrows or other impediments to egress.

(5) Gas masks with canisters affording protection against ammonia should be provided; they should be stored in some locality readily accessible to, but outside of, the room in which there is a possibility of the escape of ammonia.

(6) Every workman engaged in repair work on refrigerating appa-

[1] Chaney, Ray and St. John, J. Ind. and Eng. Chem., 1923, Vol. 15, p. 1244.
[2] Henderson, Y. and Haggard, H. W., Jour. of Ind. and Eng. Chem., June, 1922, Vol. 14, p. 548.

ratus should be required to carry a gas mask strapped to his body or hung around his neck in anticipation of the possible escape of ammonia.

(7) A valve arranged to shut off the ammonia at the storage cylinders should be placed where it can be manipulated from the outside of the building.

Protective Apparatus.

Three types of apparatus are used for protection against the inhalation of noxious gases: (1) gas masks, (2) hose masks, and (3) self-contained breathing apparatus. These three forms of apparatus differ from each other in principle, and each has advantages and disadvantages in relation to the other types. Each is best for its own special use. The greatest care should be taken to avoid inadequate or defective protective apparatus; for it may add the death of a rescuer to that of a first victim. As such apparatus, especially the rubber parts, deteriorates rapidly, it must be frequently inspected and regularly renewed.

Unfortunately there is a widely held belief that a handkerchief or some other piece of fabric, tied over the mouth and nose constitutes a gas mask. Many lives have been sacrificed to this fallacy. Fabrics that will permit the passage of the respired air will also permit the passage of noxious gases. Moistening the cloth offers protection against only a few substances and for only a short time. The more soluble irritant gases and vapors, when present only in low concentration, may be partially and temporarily absorbed by the moisture; but such makeshift arrangements offer absolutely no protection against the asphyxiants and the volatile druglike substances. Respirators designed to prevent the inhalation of dust afford no protection against noxious gases.

Gas Masks and Various Types of Canister. A properly constructed gas mask consists of a facepiece of rubber or rubberized fabric, which fits tightly across the forehead, along the cheeks and under the chin, and which is connected by a short piece of flexible and noncollapsible tube to a sheet metal canister containing absorbent materials. The facepiece is fitted with windows of nonsplintering glass placed in front of the eyes. The canister is worn suspended from the shoulders or strapped across the chest. At the bottom of the canister is a light disk check valve which opens only to admit air, so that the breath is drawn in thru the canister. A second valve opens from the facepiece to the outside air; thru this valve the breath is exhaled. The canister is filled with layers of various materials which remove, either by absorption or by chemical reaction, certain gases and vapors from the air. When the mask is fitted to the face all of the air inspired is filtered thru these materials, and is thus purified.

The gas mask in its present form is the highly developed and extremely efficient product of very extensive and careful investigation. It is light, quickly applied, allows freedom of movement, and is purchasable at a reasonable price. It affords effective protection against such gases and vapors as the materials in the canister are designed to absorb. Most canisters are charged with materials intended to absorb

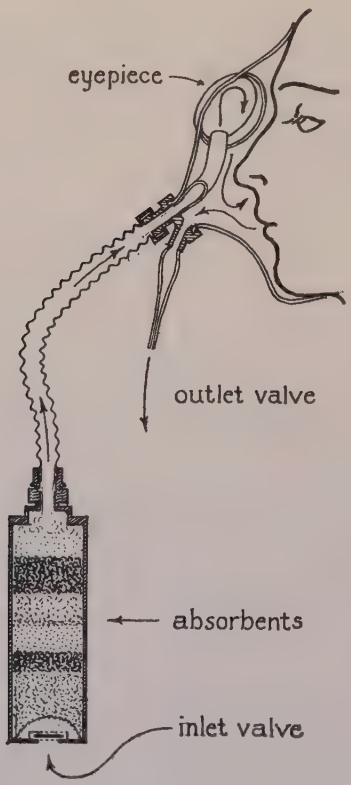


FIG. 6.—Diagram of gas mask in section.

only a limited number of closely related gases. The contaminant in the air must be known and the proper canister employed to absorb that type of gas. A canister charged to afford protection only against ammonia, for example, is useless for such gases as carbon monoxide, or hydrochloric acid fumes; for each of those gases there is a special type of absorbent. There is one type of canister, however, the so-called "all service canister," which gives protection against all gases and vapors found in industry excepting, of course, high concentrations of the simple

asphyxiants. This type of canister is useful when the contaminant in the air is unknown, as is the case when firemen enter chemical storage depots; but it has the disadvantage of a relatively short life, owing to the comparatively small supply of each absorbent in the canister, when used against any one particular gas. In most industrial plants the gases which may occur are known beforehand, and the proper canisters should be provided. Canisters filled with only one type of absorbent material afford protection for a longer time than is possible with the all service canister.

Canisters are supplied with eight main types of absorbing material.

TYPES OF CANISTER FOR PROTECTION UNDER VARIOUS CONDITIONS

Conditions	Contents of Canister	Color of Canister
(1) Protection against organic vapors, such as aniline, gasoline, benzene, ether, toluene, and the like (when not over 20 per cent in air).	600 cubic milliliters or more of activated charcoal.	Black
(2) Protection against acids such as hydrochloric, sulfur dioxide, nitrogen peroxide, chlorine and the like (not over 1 per cent in air).	600 cubic milliliters or more of soda lime or fused caustic soda.	White
(3) Protection against ammonia gas not over 3 per cent. The 3 per cent limit cannot be long endured by the wearer because of the skin irritation from the gas.	Copper sulfate and charcoal.	Green
(4) Protection against carbon monoxide (not over 3 per cent).	A mixture of metallic oxides known as "hopcalite" which catalizes the combustion of carbon monoxide with oxygen from the air and produces carbon dioxide.	Blue
(5) Protection against all of the above gases; the "all service mask."	All of the absorbents mentioned above, but only small amounts of each.	Red
(6) Protection against a combination of organic fumes and acid fumes.	Activated charcoal and soda lime.	Yellow
(7) Protection against ammonia and smoke.	Copper sulfate and charcoal with a filter pad for smoke.	Brown
(8) Protection against hydrocyanic acid gas (not over 2 per cent).	Caustic soda impregnated on pads.	With a green stripe

A stripe painted on the canister indicates that it is fitted with filter pads and will protect against smoke, dust and mists. A gas mask cannot be safely used in an atmosphere seriously deficient in oxygen. The practical limit beyond which a mask should not be used is indicated by the extinction of the flame of a candle or safety lamp. This occurs at about 17 per cent of oxygen in the air; a man is not in serious danger until the oxygen falls below 14 per cent. When, owing to an excess of the simple asphyxiant gases, the oxygen falls below this limit a gas mask ceases to afford protection, even tho the absorbent in the canister removes any actively toxic gas. Under such circumstances a hose mask or self-contained breathing apparatus must be used.

Gas masks are constructed largely of rubberized fabric, and the life of the mask while in storage is limited by the deterioration of the rubber. Gas masks should be kept in a cool, dry, dark place. It is best to store each mask in a separate box. The box is sealed with strips of gummed paper, and upon this seal is written the date at which the mask was last inspected, and the amount that the canister has been used. As it is necessary to break the seal in order to remove the mask from the box, this practice affords assurance that the canister has not been exhausted by use on some occasion which has not been recorded. If properly stored the fabric of a gas mask should last about two years; if carelessly stored its life may not be more than one year.

After a mask has been used it should be disinfected to render it safe for other users. The mask is separated from the canister, immersed in a 2 per cent solution of lysol, and then dried in the open air. When dry the eyepieces are polished, and the mask is returned to its box. Special care should be taken that there are no sharp creases or folds in the fabric.

The life of the canister depends upon the concentration of the gases to which it is subjected, the duration of exposure, and the manner in which it is stored when not in use. As supplied by the manufacturer the canister is sealed by a cap over the inlet valve and by a cork in the hose nipple. Stored in this condition and without use the canister should last a year. If air is allowed to enter, the contents of the canister deteriorate rapidly, especially if it contains soda lime or caustic soda. If a canister has been used long enough to give reason to believe that it is nearly exhausted, a fresh canister should be substituted. Most of the absorbent materials are exhausted or saturated by use, while hopcalite, the catalyst for carbon monoxide, is rendered inactive or "poisoned" by the absorption of water vapor. If the mask is to be used again, the valve opening should be capped, the cork inserted in

the upper opening of the canister, and a record made of the exposure to which it has been subjected.

The worker who uses the mask should test it for leaks before entering a contaminated atmosphere. To do this the mask is put on and tried in fresh air. The resistance to breathing should be slight, not more than an inch (25 mm.) water gage. The bottom opening is then closed with the palm of the hand and suction exerted by inhaling until the facepiece collapses. If there are no leaks this vacuum will hold for fifteen seconds. The mask is thus shown to be tight, and the wearer may proceed into the contaminated atmosphere. If fumes are noticed in the air inhaled the wearer should immediately go out into fresh air and obtain a fresh canister. Carbon monoxide has little odor, and therefore gives no indication that the canister is exhausted, or that the concentration of the gas is above the 3 per cent limit against which the blue or red canisters afford protection. It is therefore advisable to use an attachment to these masks, a breath-counting device, which indicates the approximate total time of exposure.

As an example of the extent of the protection afforded by the mask and canister, mention may be made here that the first gas mask of this type made in America was worn by one of the authors in the first test during the War, in 1917. The wearer remained for 15 minutes in an atmosphere of more than 1000 parts of chlorine per million of air. His skin wherever exposed and moist was irritated, some of his clothing was discolored and corroded, and much of the tin was dissolved off of the canister. But the wearer received not a trace of the gas in the inspired air. Since that time masks of this type have also been greatly improved and standardized.

Hose Masks. The facepiece of a hose mask is essentially the same as that of a gas mask; but instead of the inspired air entering thru a canister, it is brought in thru a length of hose, the outer end of which is supplied with fresh air. If the hose is not over 25 feet in length and the mask is tight, the force of inspiration will, without serious difficulty, draw air in against the resistance imposed by the hose. If the hose is over 25 feet in length, or if the worker must wear the mask for a considerable time, air should be blown in with a pump. In an emergency a bellows or even a jet of compressed air may be used. The latter is not to be recommended, however, for the air may contain oil. If a jet of compressed air is used, the hose should be left open at the end, and the jet should be shot in on the principle of an injector; for if the nozzle supplying the jet is inserted in the end of the hose the air pressure may blow the mask off of the wearer's face. Whenever possible the air blower for a hose mask should be of the centrifugal type, so that in case it is run at too low a speed or stops

entirely the air supply will not be cut off; for enough air may be drawn thru a centrifugal pump and even a long hose to permit the wearer of the mask to escape from an irrespirable atmosphere.

If more than one length of hose is used the couplings should be provided with locks to prevent them from unscrewing. Whenever a man wearing a hose mask enters an irrespirable atmosphere in a confined space, such, for example, as a tank car or manhole, he should wear also a safety belt to which is attached a life line extending to an attendant outside.

The hose mask is especially desirable for work in atmospheres contaminated with vapors of the lighter petroleum distillates. In such vapors the life of the canister of a gas mask is of uncertain duration, and poisoning may be rapid when the canister becomes exhausted. A

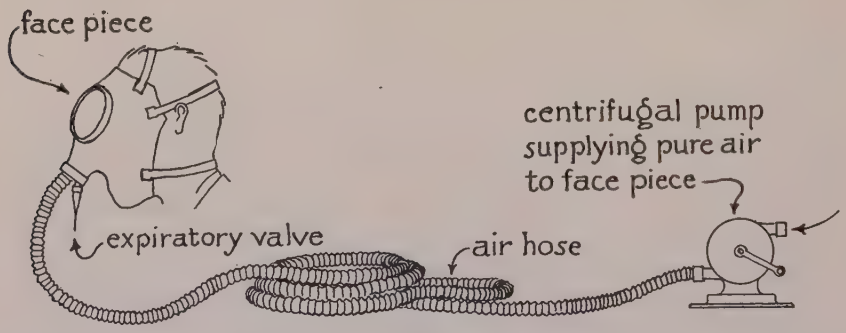


FIG. 7.—Hose mask and air pump.

self-contained breathing apparatus may also fail, for the vapors may penetrate the rubber fabric and accumulate in the circulated oxygen. A hose mask can be worn in any atmosphere regardless of oxygen content. Its only disadvantage lies in the fact that the wearer's activities are limited by the length of the hose.

Self-contained Breathing Apparatus.

A self-contained breathing apparatus is a portable device for supplying an atmosphere of oxygen, which the wearer continually rebreathes, while the carbon dioxide which he exhales is absorbed by an alkali. It consists of a facepiece or mouthpiece fitted with two valves, one inspiratory, the other expiratory. To the inspiratory valve is attached a piece of corrugated tubing leading to a bellows, or a bag of rubber fabric. A similar tube from the expiratory valve goes to a canister of soda lime, and another tube from there to the bellows or bag. The bag is automatically filled with oxygen from a cylinder of the com-

pressed gas, which is carried as part of the apparatus. The automatic feed keeps the bag at all times adequately filled by admitting more oxygen whenever the bag collapses to a certain point. When the breath is inspired, oxygen is drawn from the bag; when it is expired, the breath passes through the soda lime which removes the carbon dioxide. The purified exhaled oxygen then goes into the bellows to be reinspired. By this circulation oxygen is drawn from the cylinder only in amount sufficient to replace that consumed by the wearer.

Self-contained breathing apparatus is available in two general types;

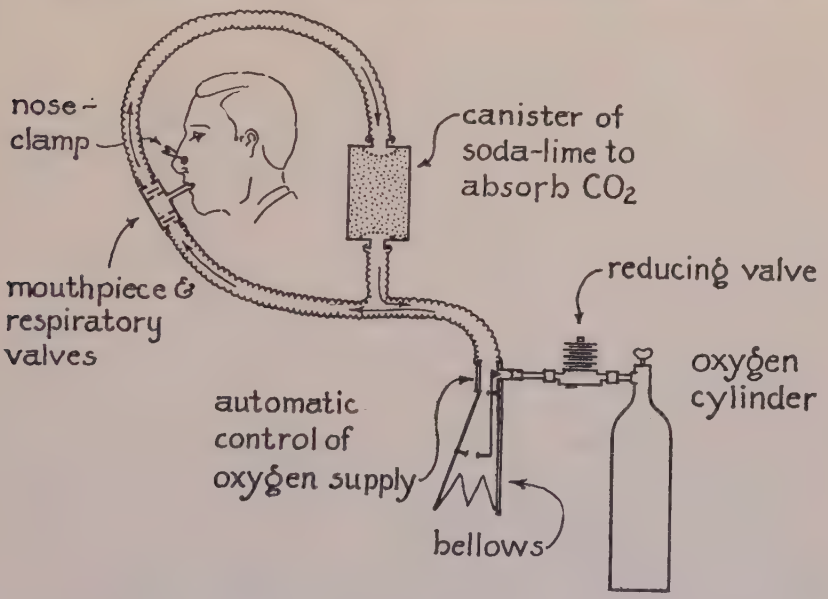


FIG. 8.—Diagram of self-contained breathing apparatus.

one can be safely used for 30 minutes, and the other for 2 hours. The first weighs from 15 to 17 pounds, and the latter 30 to 45 pounds. After the apparatus has been worn for the specified time, the cylinder of oxygen must be replaced by a new one, and the soda lime must be renewed in the canister.

Self-contained breathing apparatus has the same general application as the hose mask. It has a marked advantage over the latter in that the wearer's movements are not restricted by a long hose to the outer air; and he may therefore penetrate as far as he need into passages and chambers filled with an irrespirable atmosphere. But self-contained breathing apparatus has the disadvantage of being heavy

and cumbersome; it is expensive, and the rubber portions deteriorate rapidly. It is a complicated piece of apparatus, and for its proper operation requires frequent inspection and adjustment. The apparatus is largely used in mine rescue work and to some extent by firemen. For purposes of exploration work and rescue over considerable distances in atmospheres deficient in oxygen, where the flame of a safety lamp is extinguished, self-contained breathing apparatus is the only means available. On the other hand, for use even in very poisonous atmospheres, in which there is sufficient oxygen to support a flame, the gas mask and canister afford not only a more practical condition for the wearer to do the work for which he has come, but also a greater degree of safety; certainly with far less liability to accident. Unsuspected defects in self-contained apparatus have cost many lives; a small unnoticed crack in one of the rubber parts imposes the penalty of death. No one should ever attempt to use this form of apparatus unless he has been thoroly trained in its use and knows that his particular apparatus is in perfect order.

Treatment of Acute Poisoning by Noxious Gases.

The methods of treatment for acute poisoning have been indicated briefly in connection with the particular gases to which they apply. We will deal here with the general procedure of resuscitation. This includes two topics: (1) rescue and first aid procedures, and (2) subsequent treatment. Of these two the first is by far the more important; the life of the gassed victim is often in the hands of the first arrival, and the outcome depends upon his knowledge of the proper procedure. The doctor who treats the patient after he is taken to the hospital has far less influence on the final outcome.

Rescue.

The first step is to remove the man from the contaminated atmosphere and to bring him as rapidly as is possible into uncontaminated and preferably warm air.

A warning is necessary at this point: The rescuer must not breathe the gas himself even for a short time. No one is immune to the action of noxious gases. The well-intentioned rescuer, who walks into an atmosphere of gas and succumbs, gives no assistance to the original victim and merely adds to the work of subsequent rescuers. His action is similar to the common occurrence where a man, who himself cannot swim, jumps into deep water because he sees another man drowning. Such procedures are not heroic; they are silly. There are indeed occasional conditions in which it is possible to enter a short distance into air contaminated with gas and to drag out an unconscious

man; but the rescuer should not attempt this without having a line tied round him and held by someone outside. It is usually wiser to open the doors and windows from the outside, and to allow fresh air to sweep the gas from the room before the rescue is made.

The proper procedure for rescue, however, consists in the wearing of a suitable gas mask, hose mask, or (if fully trained in its use) a self-contained breathing apparatus, together with a belt and safety line; the line to be held by someone outside the area contaminated with gas.

First Aid Treatment.

The victim should be removed from the poisonous atmosphere and placed in fresh, but not cold air. In cold weather indoor air is preferable to outdoors. Chilling should be carefully avoided after any form of gassing, as it greatly increases the liability to subsequent pneumonia. The victim should be wrapped in blankets. Hot water bottles and heated bricks are often recommended, but they are more dangerous than beneficial in the hands of the overzealous; a man does not complain of being burned while he is unconscious, but the burns that result from hot water bottles or other heated objects placed next to the skin are in many cases the most serious sequel to the gassing.

Artificial Respiration.

Acute poisoning by anyone of the asphyxiants leads to respiratory failure. This is true also of the majority of the volatile drugs and druglike substances. Whenever breathing has ceased for this reason, artificial respiration should be started at once by the prone pressure method. The procedure of the prone pressure, or Schaefer method, is as follows:

(1) Lay the patient on his belly, one arm extended directly overhead, the other bent at the elbow, with the face turned to one side and resting on the hand or forearm, so that the nose and mouth are free for breathing.

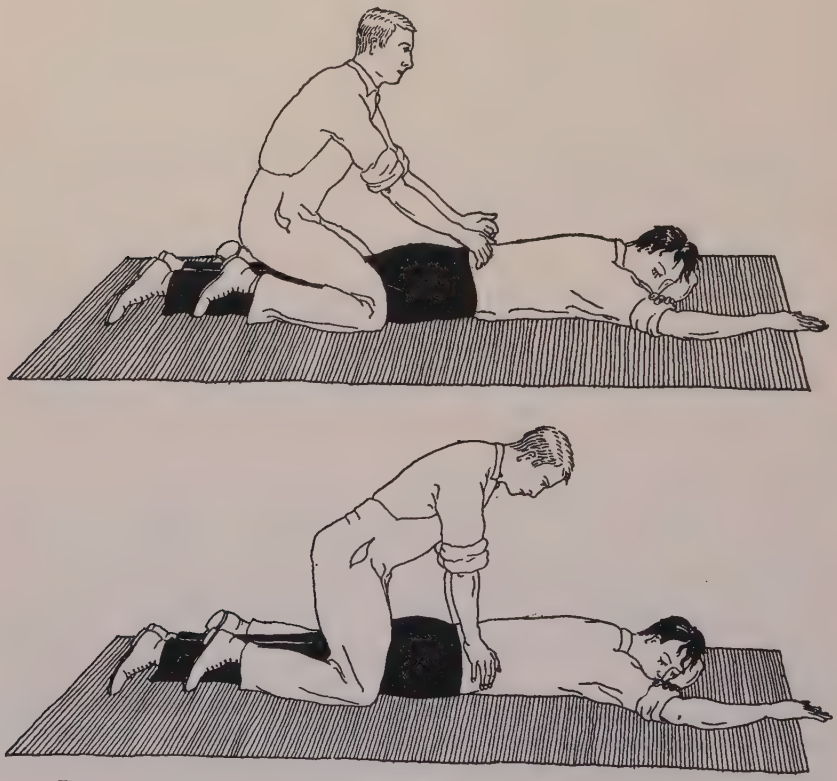
(2) Kneel straddling the patient's hips with your knees just below the patient's hipbones or opening of pants pockets. Place the palms of your hands on the small of the patient's back with fingers over the ribs; the little finger just touching the lowest rib, the thumb alongside of the fingers; the tips of the fingers just out of sight.

(3) While counting one, two, and with the arms held straight, swing forward slowly, so that the weight of your body is gradually, but not violently, brought to bear upon the patient. This act should take from two to three seconds.

(4) While counting three, swing backward so as to remove the pressure.

(5) While counting five, rest.

(6) Repeat these operations deliberately, swinging forward and backward twelve to fifteen times a minute, thus making a complete respiration in four or five seconds.



FIGS. 9 and 10.—Artificial respiration by the prone pressure method.

(7) As soon as artificial respiration has been started, and while it is being continued, an assistant should loosen all tight clothing about the patient's neck, chest, or waist and wrap the patient warmly with a blanket.

(8) Continue artificial respiration without interruption until natural breathing is restored, if necessary for several hours, or until a physician declares *rigor mortis* (stiffening of the body) has set in. Do not stop merely because he says the patient is dead; you may be able to revive him. If natural breathing stops after being restored, use this method of resuscitation again.

Manual Methods Contrasted With Mechanical Devices.

There are several types of apparatus designed to give artificial respiration. In this country the two most prominent are the pulmotor and lungmotor. Both are inferior to the manual method of artificial respiration in their effects on the patient. Both require a greater degree of training and experience than does the manual method. They have also the disadvantage that they are rarely on the spot when needed. The time which elapses between failure of respiration and the stopping of the heart is at the most only ten minutes, usually six, and often less. Time is the most essential factor in resuscitation; every minute lost after breathing has stopped, and before artificial respiration is begun, decreases the chance of recovery. Within ten minutes at most, more probably within five or less, the last chance is lost. Manual artificial respiration can be started in a few seconds by the first person who arrives at the spot where a man has been gassed. By contrast, it takes many minutes to unpack, adjust and start the mechanical devices, even in the rare instances when they are at hand. Usually they are at some distance and many minutes are lost in bringing them to the spot. Instead of immediately initiating manual artificial respiration, the rescuer waits for the device to arrive; the patient in the meantime dies. The greatest objection, however, to mechanical devices is the fact that, when reliance is placed upon them, general training in the prone pressure method is discouraged.

It is not necessary nor beneficial to the patient, but rather the reverse, to apply artificial respiration to a man who is still breathing. Nevertheless it is a common practice to put the pulmotor and lungmotor on such cases. Most men who are gassed by carbon monoxide, and who are still breathing when rescued, would recover spontaneously. But if a pulmotor or lungmotor or other mechanical device is brought, even an hour or two after the gassing, it is applied; then the claim is made in the newspapers that "the victim was resuscitated" by the apparatus. Their reputation for saving life is almost wholly derived from this type of pseudo resuscitation, aided by sensational publicity in the press and active propaganda. These devices have in fact done far more harm than good, and have led to the loss of many more lives than they have ever saved. Their use should be discouraged.

Artificial Respiration and the Physician.

Only in exceptional cases is a physician on the spot or close at hand to perform artificial respiration after poisoning by a noxious gas. The resuscitation to be effective must be carried out by the man who first reaches the victim; in a factory or mine it is a fellow workman, not a physician, who must administer first aid. If breathing has stopped

and artificial respiration is delayed until a physician can arrive, death results in the meantime. Physicians, and particularly surgeons and anesthetists, have occasionally to perform artificial respiration when respiratory failure occurs during anesthesia. With the patient lying on his back on a narrow operating table it is not convenient to apply the prone pressure method; so the less effective Sylvester method is generally used. These are the only resuscitations that medical men usually see, and as they are not called upon to perform artificial respiration by the prone pressure method they are as a rule unfamiliar with the method.

When the physician arrives at the scene of an accident he assumes authority. But his lack of training in the best modern method often leads to deplorable results. A physician who sees many deaths following illness comes to think that when respiration stops the patient is dead; for this is the case in most of the diseases. But it is not true under three important conditions: namely, gas poisoning, drowning and electric shock. In these conditions the vital engine is merely stalled and needs to be started again, or, as an automobilist would say, cranked. It is nowadays a rather frequent occurrence for the victim of one of these accidents, who might be restored, to be declared dead by a doctor, or to be sent to a hospital in an ambulance; and he arrives dead. Fortunately in some cases an electric lineman or other workman, or a boy scout persists in administering prone pressure artificial respiration, and thus restores life.

Inhalational Treatment.

For many years the inhalation of oxygen has been the treatment generally advocated for poisoning by many of the noxious gases and vapors, and particularly for carbon monoxide poisoning. Oxygen has, however, one serious drawback; it is to some extent a respiratory depressant. The depressing action is not usually evident when oxygen is inhaled by a man who is breathing normally, but it nevertheless forms a definite, altho slight, handicap to the full return of spontaneous breathing when given during artificial respiration or depressed natural breathing.

This disadvantage of oxygen is overcome by the addition of 5 per cent of carbon dioxide. Carbon dioxide is the natural stimulus to breathing. Many cases of respiratory failure induced by the inhalation of noxious gases involve a considerable element of apnea vera owing to the reduction of the normal amount of carbon dioxide in the blood. The inhalation of carbon dioxide, not only supplies the deficient carbon dioxide, but gives an added stimulus to the depressed center of respira-

tion. It increases the volume of breathing, and—what is equally important—does this in an entirely normal manner.

Thus inhalation of carbon dioxide greatly expedites the elimination of volatile substances from the body. The procedure was introduced by the authors a few years ago, and has come into extensive use for the treatment of carbon monoxide poisoning. It is also generally used to hasten the elimination of anesthetics after surgical operations; it shortens and lessens the distressing postanesthetic nausea and cyanosis. It is applicable to poisoning by any volatile substance other than irritants, as, for example, alcoholic drunkenness, and is an effective aid during artificial respiration. The inhalation of the mixture of oxygen

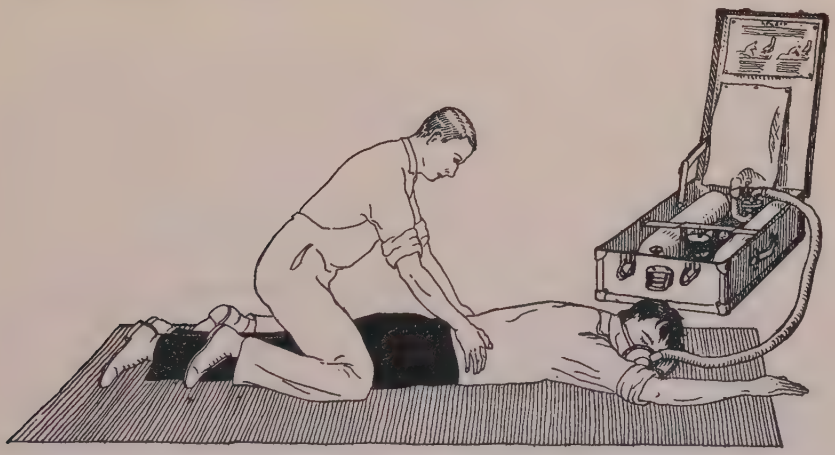


FIG. 11.—Inhalation combined with artificial respiration.

and 5 per cent carbon dioxide is given for a period of 20 to 30 minutes as soon after the man is removed from the gas as possible, and if artificial respiration is necessary, during that period also, as it assists in initiating spontaneous breathing. Aside from its stimulating action upon breathing, carbon dioxide increases the action of the heart and stimulates the circulation. It is, next to artificial respiration itself, the most useful measure in resuscitation. Experience demonstrates that it has no ill effects; for the stimulation is of a mild and essentially physiological character.

The mixture of carbon dioxide and oxygen is now available in cylinders of the compressed gases from all manufacturers of oxygen. To be effective the oxygen and carbon dioxide mixture (which is often sold under the trade name of carbogen) must be administered with a specially designed inhalator. It is useless to try to give an inhalation

with a funnel held above the face or any such makeshift. The so-called H. H. Inhalator was designed by the authors to administer the mixture of oxygen and carbon dioxide. The apparatus consists of cylinders of the mixed gas opening into a reducing valve; from this valve the gas is passed under low pressure thru a calibrated needle valve, and then into a collapsible reservoir bag. From this bag the gas is inhaled thru a rubber tubing attached to a mask held tightly over the patient's face. A check valve opening outward on the facepiece allows the escape of expired air; a lightly weighted check valve placed near the collapsible bag permits the entrance of outside air in case the

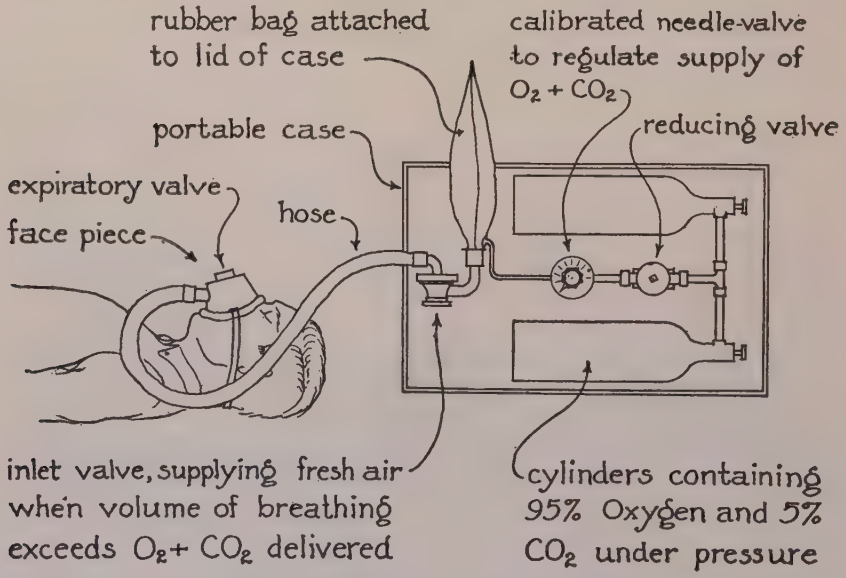


Fig. 12.—Diagram of H-H Inhalator.

patient breathes a larger volume than that of the gas passed at the setting of the calibrated needle valve. The air inlet valve has the advantage also of preventing the volume of breathing from becoming excessive; for when the volume of breathing exceeds the flow of gas, air enters, dilutes the carbon dioxide and diminishes the respiratory stimulation.

In using this inhalator the valve at the top of the steel bottle (or bottles, for there are usually two) containing the mixed gas is opened, and the pointer of the calibrated needle valve is set at zero. The mask is then put over the patient's face; the lower part well down on the chin and the upper pressed firmly over the nose. As soon as the mask is properly applied the needle valve is turned to admit the mixture of

oxygen and carbon dioxide into the bag, and so to the mask, at a rate at first of 5 or 6, and then of 10 liters per minute. If the man breathes less than the amount fed, the bag stays full; if he breathes more, the bag collapses. As the inhalation proceeds and the volume of breathing increases, the valve is adjusted so that the bag does not quite collapse at each breath. As the stimulating action of the carbon dioxide comes into play, the volume of breathing is increased to 20 or 30 liters. It does not appreciably exceed this volume for the reason that this is the maximum that the inhalator supplies; if the breathing rises above this volume outside air is admitted thru the check valve below the bag, and the stimulus to respiration is thus automatically kept from increasing further.

Medication and After Treatment.

The inhalational treatment described in the preceding section is a specific therapy for a wide range of intoxications. Other forms of medication are of little use in the immediate treatment of poisoning by noxious gases and vapors; none are specific.

The transfusion of blood is effective in poisoning by the organic nitrogen compounds and arsine. Transfusion has also been used for carbon monoxide poisoning, but it is of no benefit unless performed during the first hour after the removal from the gas; and it is in fact never performed so soon. At later periods the elimination of carbon monoxide has already progressed to a point which renders transfusion unnecessary; the condition of the patient is then wholly the expression of the secondary effects of asphyxia, for which transfusion is useless. The intravenous injection of hypertonic saline is of more use in relieving the headache and other symptoms. Bleeding, alone or combined with infusion of saline, has been suggested as a measure of relief in edema of the lungs caused by irritants.

While most forms of medication are of no benefit in poisoning by noxious gases, some are positively harmful. All first aid workers should be warned never under any circumstances to give anything by mouth to an unconscious man. An unconscious man cannot swallow and the fluid often runs into the trachea and chokes him. Alcohol in any form is likewise contraindicated; this is particularly true in asphyxia or in poisoning by the anesthetic hydrocarbons. Alcohol intensifies both of these conditions. Both the layman and the physician should remember that while treatment, however well intended, does little good, it may easily do great harm. Especially after exposure to an irritant gas absolute rest is essential; the slightest movement may cause death.

Amyl nitrite has been employed in resuscitation, but it is harmful; the respiratory stimulation which it induces results from a fall in blood

pressure. Emetics have been given in gas poisoning, but such a procedure is obviously useless when the toxic substance has been absorbed thru the lungs. It is probable that no hypodermic injection of any known drug is of the slightest benefit in gas poisoning, or in general in first aid for accidents involving cessation of respiration. The common injection is one of camphor dissolved in ether; it is certainly not beneficial, and is probably sometimes distinctly harmful.

Harmful Practices.

The zealous first aid worker frequently feels that he must be continually doing something to aid the poisoned man. While the intentions are commendable, the results are often deplorable; such, for example, as tearing the victim's nose off by rubbing his face against a sharp stone or rough planking, or breaking his legs or ribs for the sake of the stimulus of "countershock." First and foremost the resuscitator must be gentle; he must remember that he is dealing with a human being who may recover and will not wish to be maimed by his treatment. Next, he should follow the general directions and principles set forth above. If he feels that he must do something more, he may give the patient a cup of black coffee, but only after consciousness is fully restored.

Under no circumstances should a man who has been gassed be allowed to exercise. He must neither walk nor even sit up, but must be kept recumbent and as quiet as possible until all symptoms have passed off.

In concluding this discussion of practices which are contraindicated in poisoning by noxious gases and vapors, especial mention must be made of the most reprehensible of all: countershock. Countershock consists in the application of external stimuli to the body as a means of restoring breathing and consciousness. Throwing cold water over a man who is gassed is a form of countershock. Cold water douches have only one place in first aid treatment and that is for sunstroke. In gas poisoning they greatly increase the liability to pneumonia. The inhalation of dilute ammonia, or smelling salts, is a harmless, but unbeneficial, form of countershock. The most brutal form of countershock practised is the beating of the unconscious victim on the soles of the feet with an axe or other heavy instrument; a procedure similar to that used by policemen to awaken tramps. Manual punishment is not resuscitation; it is sufficiently difficult to make the enthusiastic first aid worker be gentle without suggesting to him that he beat his victim into consciousness. The picture here drawn of the methods of "resuscitation" as sometimes practised is not overcolored, but is in accord with rather common actual occurrences.

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Note on the Actions of Noxious Gases upon Plants.

Plants, and particularly trees, are well known to be injuriously affected, or even killed, by the low concentrations of industrial fumes in which large numbers of people in cities live. While they are comparatively insensitive to certain gases, plants are more susceptible than animals to others. Around smelters and other factories producing acid vapors the trees may be killed for considerable distances, the effects depending upon the prevailing direction of the wind, height of chimneys, and topography of the neighborhood. Thus forests on hills around a factory town in a valley may be destroyed. In coal smoke the actively injurious agent is sulfur dioxide, or rather the sulfuric acid into which sulfur dioxide changes in the presence of water vapor. In Germany forests have sometimes suffered severely from the smoke from locomotives of a railroad with heavy traffic running thru a valley. Conifers appear to be particularly sensitive. One part of sulfuric acid per million of air may produce noticeable effects. The ill effects are said to be produced only during the time that sunlight is also acting; that is, the fumes act only during photosynthesis.

The other principal gas hazard of vegetation is that due to illuminating gas leaking from the mains under the streets of cities. The poisonous constituent is not carbon monoxide but ethylene. The action upon growing plants appears to be largely thru absorption by the roots. The effects are particularly noticeable in greenhouses into which there is even a slight leak of gas. The odor of the illuminating gas may be absorbed in the ground, and the first effect noticed may be

upon the flowers. Twelve parts of illuminating gas in a million of air cause the already open buds of carnations to close in the course of twelve hours, thus inducing the so-called sleep of these flowers. Twenty-five parts of illuminating gas in a million of air are sufficient to kill many hothouse plants in the course of a few days. The amount of ethylene, the active agent, involved in these effects is of the order of one part or less in a million of air.

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